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Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

(54) 9-Oxa-Epothilon-Derivate, Verfahren zu deren Herstellung sowie ihre Verwendung in pharmazeutischen Präparaten

(57) Die vorliegende Erfindung beschreibt neue Epothilon-Derivate, die durch ein Sauerstoffatom in der Position 9 des Epothilon-Grundgerüstes gekennzeichnet sind.
Die neuen Verbindungen interagieren mit Tubulin, idem sie gebildete Mikrotubuli stabilisieren. Sie sind in der Lage, die Zellteilung phasenspezifisch zu beeinflussen und sind zur Behandlung maligner Tumoren geeignet, beispielsweise Ovarial-, Magen-, Colon-, Adeno-, Brust-, Lungen-, Kopf- und Nacken-Karzinome, malignes Melanom, akute lymphozytäre und myelocytäre Leukämie. Außerdem sind sie zur Anti-Angiogenese-Therapie sowie zur Behandlung chronischer entzündlicher Erkrankungen (Psoriasis, Arthritis) geeignet. Zur Vermeidung unkontrollierter Zellwucherungen an sowie der besseren Verträglichkeit von medizinischen Implantaten lassen sie sich in polymere Materialien auf- bzw. einbringen.
Die erfindungsgemäßen Verbindungen können alleine oder zur Erzielung additiver oder synergistischer Wirkungen in Kombination mit weiteren in der Tumortherapie anwendbaren Prinzipien und Substanzklassen verwendet werden.

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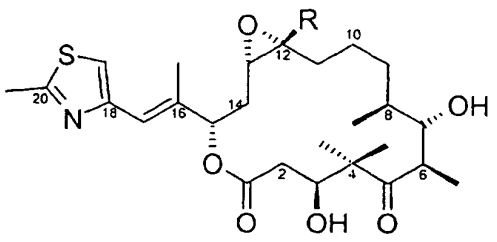
Beschreibung

[0001] Von Höfle et al. wird die cytotoxische Wirkung der Naturstoffe Epothilon A (R = Wasserstoff) und Epothilon B (R = Methyl)



Epothilon A (R = H), Epothilon B ($R=CH_3$)

z. B. in Angew. Chem. 1996, 108, 1671–1673, beschrieben. Wegen der in-vitro-Selektivität gegenüber Brust- und Darmzelllinien und ihrer im Vergleich zu Taxol deutlich höheren Aktivität gegen P-Glycoprotein-bildende, multiresistente Tumorlinien sowie ihre gegenüber Taxol verbesserten physikalischen Eigenschaften, z. B. eine um den Faktor 30 höhere Wasserlöslichkeit, ist diese neuartige Strukturklasse für die Entwicklung eines Arzneimittels zur Therapie maligner Tumoren besonders interessant.

[0002] Die Naturstoffe sind sowohl chemisch als auch metabolisch für eine Arzneimittelentwicklung nicht ausreichend stabil. Zur Beseitigung dieser Nachteile sind Modifikationen an dem Naturstoff nötig. Derartige Modifikationen sind nur auf totalsynthetischem Wege möglich und setzen Synthesestrategien voraus, die eine breite Modifikation des Naturstoffes ermöglichen. Ziel der Strukturveränderungen ist es auch, die therapeutische Breite zu erhöhen. Dies kann durch eine Verbesserung der Selektivität der Wirkung und/oder eine Erhöhung der Wirkstärke und/oder eine Reduktion unerwünschter toxischer Nebenwirkungen, wie sie in Proc. Natl. Acad. Sci. USA 1998,9S,9642–9647 beschrieben sind, erfolgen.

[0003] Die Totalsynthese von Epothilon A ist von Schinzer et al. in Chem. Eur. J. 1996, 2, No. 11, 1477–1482 und in Angew. Chem. 1997, 109, Nr. 5, S. 543–544 beschrieben.

[0004] Epothilon-Derivate wurden bereits von Höfle et al. in der WO 97/19086 beschrieben. Diese Derivate wurden ausgehend vom natürlichen Epothilon A oder B hergestellt. Auch Epothilon C und D (Doppelbindung zwischen den Kohlenstoffatomen 12 und 13: Epothilon C = Desoxyepothilon A; Epothilon D = Desoxyepothilon B) sind als mögliche Ausgangsprodukte hierfür beschrieben.

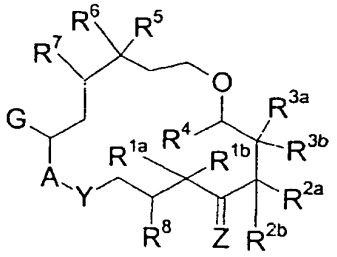
[0005] Eine weitere Synthese von Epothilon und Epothilonderivaten wurde von Nicolaou et al. in Angew. Chem. 1997, 109, Nr. 1/2, S. 170–172 beschrieben. Die Synthese von Epothilon A und B und einiger Epothilon-Analoga wurde in Nature, Vol. 387, 1997, S. 268–272, die Synthese von Epothilon A und seinen Derivaten in J. Am. Chem. Soc., Vol. 119, No. 34, 1997, S. 7960–7973 sowie die Synthese von Epothilon A und B und einiger Epothilon-Analoga in J. Am. Chem. Soc., Vol. 119, No. 34, 1997, S. 7974–7991 ebenfalls von Nicolaou et al. beschrieben.

[0006] Ebenfalls Nicolaou et al. beschreiben in Angew. Chem. 1997, 109, Nr. 19, S. 2181–2187 die Herstellung von Epothilon A-Analoga mittels kombinatorischer Festphasensynthese. Auch einige Epothilon B-Analoga sind dort beschrieben.

[0007] Epothilon-Derivate, z. T. auch Epothilon C und D, sind des weiteren in den Patentanmeldungen WO 99/07692, WO 99/02514, WO 99/01124, WO 99/67252, WO 98/25929, WO 97119086, WO 98/38192, WO 99/22461 und WO 99/58534 beschrieben.

[0008] Die Aufgabe der vorliegenden Erfindung besteht darin, neue Epothilon-Derivate zur Verfügung zu stellen, die sowohl chemisch als auch metabolisch für eine Arzneimittelentwicklung ausreichend stabil sind und die hinsichtlich ihrer therapeutischen Breite, ihrer Selektivität der Wirkung und/oder unerwünschter toxischer Nebenwirkungen und/oder ihrer Wirkstärke den natürlichen Derivaten überlegen sind.

[0009] Die vorliegende Erfindung beschreibt die neuen Epothilon-Derivate der allgemeinen Formel I,

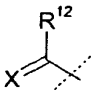


I,

worin

R^{1a}, R^{1b} gleich oder verschieden sind und Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, oder gemeinsam eine -

$(CH_2)_m$-Gruppe mit m = 1, 2, 3, 4 oder 5, oder eine -(CH_2)-O-(CH_2)-Gruppe,
R^{2a}, R^{2b} gleich oder verschieden sind und Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, -$(CH_2)_r$-C≡C-$(CH_2)_p$-R^9, -$(CH_2)_r$-C=C-$(CH_2)_p$-R^9,
r gleich 0 bis 4,
p gleich 0 bis 3,
R^9 Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, C_1-C_{10}-Acyl, oder, falls p>0 ist, auch eine Gruppe OR^{10},
R^{10} Wasserstoff, eine Schutzgruppe PG^{10},
R^{3a} Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl,
R^{3b} OH, OPG^3
R^4 Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl
R^5 Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Arallkyl, Halogen, Cyano, $(CH_2)_s$-T, wobei s für 1, 2, 3 oder 4,
T für OR^{11} oder Hal,
R^{11} für Wasserstoff oder PG^{11} stehen,
R^6, R^7 je ein Wasserstoffatom, gemeinsam eine zusätzliche Bindung oder ein Sauerstoffatom,
G eine Gruppe



ein bi- oder tricyclischer Arylrest,
R^{12} Wasserstoff, Halogen, CN, C_1-C_{20}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, die alle substituiert sein können,
X ein Sauerstoffatom, zwei Alkoxygruppen OR^{13}, eine C_2-C_{10}-Alkylen-α,ω-dioxygruppe, die geradkettig oder verzweigt sein kann, H/OR^{14} oder eine Gruppierung $CR^{15}R^{16}$,
wobei
R^{13} für einen C_1-C_{20}-Alkylrest,
R^{14} für Wasserstoff oder eine Schutzgruppe PG^{14},
R^{15}, R^{16} gleich oder verschieden sind und für Wasserstoff, einen C_1-C_{20}-Alkyl-, Aryl-, C_7-C_{20}-Aralkylrest stehen,
A-Y eine Gruppe O-C(=O), O-CH_2, CH_2C(=O), NR^{17}-C(=O), NR^{17}-SO_2,
R^{17} Wasserstoff, C_1-C_{10}-Alkyl,
Z ein Sauerstoffatom oder H/OR^{18},
wobei
R^{18} Wasserstoff oder eine Schutzgruppe PG^{18} ist,
R^8 OH oder OPG^8
Hal Halogen, vorzugsweise Fluor, Chlor oder Brom bedeutet
ausgenommen derjenigen Verbindungen, in denen R^{2a} Wasserstoff ist und R^{2b} Wasserstoff, Alkyl oder Aryl und gleichzeitig
R^5 Wasserstoff, Alkyl oder Aryl und gleichzeitig
A-Y eine Gruppierung O-C(=O), O-CH_2 oder NR^{17}-C(=O) und gleichzeitig
G einen bi- oder tricyclischen Arylrest oder eine Gruppierung X=(CR^{12})- bedeuten, wobei alle anderen Reste die angegebenen Bedeutungen haben können.

[0010] Durch den Disclaimer werden die in der WO 99/02514 beanspruchten Verbindungen ausgeschlossen.

[0011] Die nachstehend genannten Verbindungen sind erfindungsgemäß bevorzugt:
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
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(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa16-(1-chlor-2-(2-pyridyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-7-ethyl-16-(1-chlor-2-(2-pyridyl)ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-chlor-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-chlor-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-pyridyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-7-ethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-7-ethyl-16-(1-chlo r-2-(2-methyloxazol-4-yl)ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-pyridyl)ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-7-ethyl-16-(1-chlor-2-(2-pyridyl)ethenyl)-1 -aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-chlor-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-pyridyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-7,9,13-trimethyl-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-deca-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-7-ethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-10-ethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-deca-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-7,9,13-trimethyl-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-deca-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-7-ethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-10-ethy(-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-7,9,13-trimethyl-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-deca-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-7-ethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-10-ethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy1,10-dioxa-9,13-dimethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion

4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-7,9,13-trimethyl-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-deca-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-7-ethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-10-ethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramelhyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16 R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyciohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazoly(ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-imethyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-mehhyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0] heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexa dec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-1 2,1 6-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S, 10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(but-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(but-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion (1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(11-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-5-benzoxazolyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dibydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-1 3-en-2,6-dion
(1S,3S(Z),7S, 10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5, 5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-en-1-yl)-1-aza-10-

oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z])-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(but-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,5S, 9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-in-1-yl)-5,5-(1,3-trimethylen)cydohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,1 2R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,1 6-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-5-benzothiazolyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-en-1-y1)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5- benzothiazolyl)-7-(but-2-in-1-yl)-5,5,9,13-tet-

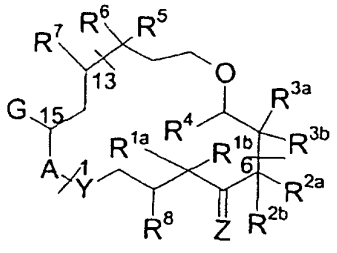
ramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-in-1-y1)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo(14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-13-fluor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-13-fluor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Fluor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Fluor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-13-chlor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-13-chlor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-ethyl-13-fluor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Fluor-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Fluor-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-allyl-13-chlor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Chlor-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Chlor-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-13-chlor-16-(1-methyl-2-(2-methyl-2-pyridyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-trimethylen-1,10-dioxa-7,9-dimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-trimethylen-1,10-dioxa-7,9-dimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-trimethylen-1,10-

dioxa-7,9-dimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4,13,17-trioxabicyclo[14.1. 0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-4-oxazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-oxazolyl)enyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-oxazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-2-pyridyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-7-ethyl-13-chlor-16-(1-chlor-2-(2-methyl-2-pyridyl)ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-7-ethyl-3-(1-chlor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-7-ethyl-3-(1-chlor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-13-fluor-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-13-fluor-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Fluor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Fluor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-13-chlor-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-13-chlor-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-7-ethyl-13-chlor-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-7-allyl-13-chlor-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-13-fluor-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-13-fluor-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Fluor-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Fluor-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-13-chlor-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-13-chlor-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-13-fluor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-

5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-13-fluor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Fluor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Fluor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-13-chlor-1 (3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-13-chlor-1 (3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-ethyl-13-fluor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Fluor-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Fluor-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-allyl-13-chlor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-101-oxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Chlor-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Chlor-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-13-chlor-16-(1-methyl-2-(2-methyl-2-pyridyl)ethenyl)-1-aza-10-oxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S, 16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-trimethylen-1-aza-10-oxa-7,9-dimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S, 16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S, 16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,5S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-trimethylen-1-aza-10-oxa-7,9-dimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S, 16S)-16-Chlor-7,11-dihydroxy-3(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-4-oxazolyl)ethenyl)-1-aza-10-oxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-oxazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-oxazolyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-2-pyridyl)ethenyl)-1-aza-10-oxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetra-

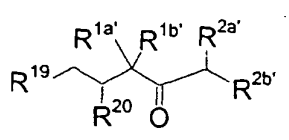
methyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-7-ethyl-13-chlor-16-(1-chlor-2-(2-methyl-2-pyridyl)ethenyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-7-ethyl-3-(1-chlor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-7-ethyl-3-(1-chlor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-13-fluor-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-13-fluor-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Fluor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Fluor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-13-chlor-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-13-chlor-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-7-ethyl-13-chlor-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-7-allyl-13-chlor-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-13-fluor-16-(2-methyl-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-13-fluor-16-(2-methyl-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Fluor-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Fluor-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S)-4,8-Dihydroxy-13-chlor-16-(2-methy(-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-13-chlor-16-(2-methyl-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S,7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S,7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion

[0012] Die Darstellung der neuen Epothilon-Derivate, in denen R^5 nicht Halogen oder Cyano ist, basiert auf der Verknüpfung dreier Teilfragmente A, B und C. Die Schnittstellen liegen wie in der allgemeinen Formel I' angedeutet.



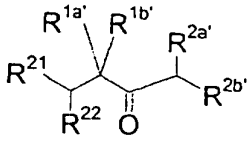
I',

A bedeutet ein C_1-C_6-Fragment (Epothilon-Zählweise) der allgemeinen Formel A-1 oder A-2



A-1

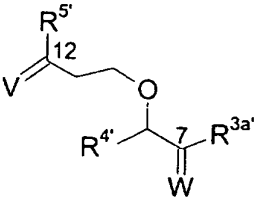
oder



A-2,

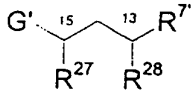
worin
$R^{1a'}$, $R^{1b'}$, $R^{2a'}$ und $R^{2b'}$ die bereits für R^{1a}, R^{1b}, R^{2a} und R^{2b} genannten Bedeutungen haben und
R^{19} CH_2OR^{19a}, CH_2-Hal, CHO, CO_2R^{19b}, COHal,
R^{20} Wasserstoff, OR^{20a}, Hal, OSO_2R^{20b},
R^{19a}, R^{20a} Wasserstoff, SO_2-Alkyl, SO_2-Aryl, SO_2-Aralkyl oder gemeinsam eine $-(CH_2)_o$-Gruppe oder gemeinsam eine $CR^{23a}R^{23b}$-Gruppe,
R^{19b}, R^{20b} Wasserstoff, C_1-C_{20}-Alkyl, Aryl, C_1-C_{20}-Aralkyl,
R^{23a}, R^{23b} gleich oder verschieden sind und Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, oder gemeinsam eine $-(CH_2)_q$-Gruppe,
o 2 bis 4,
q 3 bis 6,
R^{21} Wasserstoff,
R^{22} Hydroxyl, oder
R^{21}, R^{22} gemeinsam ein Sauerstoffatom, oder eine C_2-C_{10}-Alkylen-α,ω-dioxygruppe, die geradkettig oder verzweigt sein kann,
R^{21}, R^{22} jeweils eine C_1-C_{10}-Alkoxygruppe,
einschließlich aller Stereoisomeren sowie deren Gemische bedeuten sowie
freie Hydroxylgruppen in R^{19}, R^{20} und R^{22} verethert oder verestert, freie Carbonylgruppen in A-1 bzw A-2 ketalisiert, in einen Enolether überführt oder reduziert sowie freie Säuregruppen in A-1 bzw A-2 in deren Salze mit Basen überführt sein können.

[0013] B steht für ein C_7-C_{12}-Fragment (Epothilon-Zählweise) der allgemeinen Formel



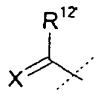
B

worin
$R^{3a'}$, $R^{4'}$ und $R^{5'}$ die bereits für R^{3a}, R^4 und R^5 (außer $R^{5'}$ = Hal, CN) genannten Bedeutungen haben, und
V ein Sauerstoffatom, zwei Alkoxygruppen OR^{23}, eine C_2-C_{10}-Alkylen-α,ω-dioxygruppe, die geradkettig oder verzweigt sein kann oder H/OR^{24},
W ein Sauerstoffatom, zwei Alkoxygruppen OR^{25}, eine C_2-C_{10}-Alkylen-α,ω-dioxygruppe, die geradkettig oder verzweigt sein kann oder H/OR^{26},
R^{24}, R^{26} unabhängig voneinander Wasserstoff oder eine Schutzgruppe PG^{24},
R^{23}, R^{25} unabhängig voneinander C_1-C_{20}-Alkyl,
bedeuten.
C steht für ein C_{13}-C_{16}-Fragment (Epothilon-Zählweise) der allgemeinen Formel



C

worin
G' eine Gruppe

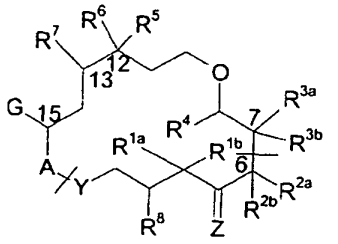


,

ein bi-oder tricyclischer Arylrest,
R^{12} die bereits in der allgemeinen Formel I für R^{12} genannte Bedeutung hat und

R^7 ein Wasserstoffatom,
R^{27} Halogen, N_3, NHR^{29}, eine Hydroxygruppe, eine geschützte Hydroxygruppe O-PG^{27}, eine geschützte Aminogruppe $NR^{29}PG^{27}$, eine C_1-C_{10}-Alkylsulfonyloxygruppe, die gegebenenfalls perfluoriert sein kann, eine gegebenenfalls durch C_1-C_4-Alkyl, Nitro, Chlor oder Brom substituierte Benzoyloxy-Gruppe, eine $NR^{29}SO_2CH_3$-Gruppe, eine $NR^{29}C(=O)CH_3$-Gruppe, eine CH_2-C(=O)-CH_3-Gruppe,
R^{28} eine Hydroxygruppe, Halogen, eine geschützte Hydroxygruppe OPG^{28}, ein Phosphoniumhalogenidrest $PPh_3{}^+Hal^-$ (Ph = Phenyl; Hal = F, Cl, Br, I), ein Phosphonatrest P(O)(OQ)$_2$ (Q = C_1-C_{10}-Alkyl oder Phenyl) oder ein Phosphinoxidrest P(O)Ph_2 (Ph = Phenyl),
X ein Sauerstoffatom, zwei Alkoxygruppen $OR^{13'}$, eine C_2-C_{10}-Alkylen-α,ω-dioxygruppe, die geradkettig oder verzweigt sein kann, H/$OR^{14'}$ oder eine Gruppierung $CR^{15'}R^{16'}$,
wobei
$R^{13'}$ für einen C_1-C_{20}-Alkylrest,
$R^{14'}$ für Wasserstoff oder eine Schutzgruppe PG^{14},
$R^{15'}$, $R^{16'}$ gleich oder verschieden sind und für Wasserstoff, einen C_1-C_{20}-Alkyl-, Aryl-, C_7-C_{20}-Aralkylrest stehen,
bedeuten.

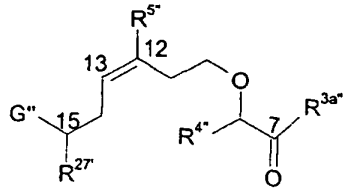
[0014] Die Darstellung der neuen Epothilon-Derivate, in denen R^5 gleich Halogen oder Cyano ist, basiert auf der Verknüpfung zweier Teilfragmente A und D. Die Schnittstellen liegen wie in der allgemeinen Formel I" angedeutet.



I"

[0015] A entspricht hierbei dem bereits beschriebenen C_1-C_6-Fragment (Epothilon-Zählweise) der allgemeinen Formel A-1 oder A-2.

[0016] D steht für ein C_7-C_{15}-Fragment (Epothilon-Zählweise) der allgemeinen Formel



D

worin
$R^{5"}$ für Halogen oder Cyano steht und $R^{3a"}$, $R^{4"}$, $R^{27"}$ und G" die bereits für R^{3a}, R^4, R^{27} und G genannten Bedeutungen haben.

[0017] Als Alkylgruppen R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^4, R^5, R^9, R^{12}, R^{13}, $R^{13'}$, R^{15}, $R^{15'}$, R^{16}, $R^{16'}$, R^{19b}, R^{20b}, R^{23}, R^{25} sind gerad- oder verzweigtkettige Alkylgruppen mit 1–20 Kohlenstoffatomen zu betrachten, wie beispielsweise Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, tert.-Butyl, Pentyl, Isopentyl, Neopentyl, Heptyl, Hexyl, Decyl. Die Alkylgruppen R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^4, R^5, R^9, R^{12}, R^{13}, $R^{13'}$, R^{15}, $R^{15'}$, R^{16}, $R^{16'}$, R^{19b}, R^{20b}, R^{23}, R^{23a}, R^{23b}, R^{25} können perfluoriert oder substituiert sein durch 1–5 Halogenatome, Hydroxygruppen, C_1-C_4-Alkoxygruppen, C_6-C_{12}-Arylgruppen (die durch 1–3 Halogenatome substituiert sein können).

[0018] Als Arylrest R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^4, R^5, R^9, R^{12}, R^{15}, $R^{15'}$, R^{16}, $R^{16'}$, R^{19b}, R^{20b}, R^{23a}, R^{23b} kommen substituierte und unsubstituierte carbocyclische oder heterocyclische Reste mit einem oder mehreren Heteroatomen wie z. B. Phenyl, Naphthyl, Furyl, Thienyl, Pyridyl, Pyrazolyl, Pyrimidinyl, Oxazolyl, Pyridazinyl, Pyrazinyl, Chinolyl, Thiazolyl, Benzothiazolyl, Benzoxazolyl, die einfach oder mehrfach substituiert sein können durch Halogen, OH, O-Alkyl, CO_2H, CO_2-Alkyl, -NH_2, -NO_2, -N_3, -CN, C_1-C_{20}-Alkyl, C_1-C_{20}-Acyl, C_1-C_{20}-Acyloxy-Gruppen, in Frage.

[0019] Als bi- und tricyclische Arylreste G kommen substituierte und unsubstituierte carbocyclische oder heterocyclische Reste mit einem oder mehreren Heteroatomen wie z. B. Naphthyl, Anthryl, Benzothiazolyl, Benzoxazolyl, Benzimidazolyl, Chinolyl, Isochinolyl, Benzoxazinyl, Benzofuran, Indolyl, Indazolyl, Chinoxalinyl, Tetrahydroisochinolinyl, Tetrahydrochinolinyl, Thienopyridinyl, Pyridopyridinyl, Benzopyrazolyl, Benzotriazolyl, Dihydroindolyl, die einfach oder mehrfach substituiert sein können durch Halogen, OH, O-Alkyl, CO_2H, CO_2-Alkyl, -NH_2, -NO_2, -N_3, -CN, C_1-C_{20}-Alkyl, C_1-C_{20}-Acyl, C_1-C_{20}-Acyloxy-Gruppen, in Frage.

[0020] Die Aralkylgruppen in R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^4, R^5, R^9, R^{12}, R^{15}, $R^{15'}$, R^{16}, $R^{16'}$, R^{19b}, R^{20b}, R^{23a}, R^{23b} können im Ring bis 14 C-Atome, bevorzugt 6 bis 10 und in der Alkylkette 1 bis 8, bevorzugt 1 bis 4 Atome enthalten. Als Aralkylreste kommen beispielsweise in Betracht Benzyl, Phenylethyl, Naphthylmethyl, Naphthylethyl, Furylmethyl, Thienylethyl, Pyridylpropyl. Die Ringe können einfach oder mehrfach substituiert sein durch Halogen, OH, O-Alkyl, CO_2H,

CO_2-Alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-Alkyl, C_1-C_{20}-Acyl, C_1-C_{20}-Acyloxy-Gruppen.

[0021] Die in R^{21}, R^{22} und X in der allgemeinen Formel I enthaltenen Alkoxygruppen sollen jeweils 1 bis 20 Kohlenstoffatome enthalten, wobei Methoxy-, Ethoxy-, Propoxy-, Isopropoxy- und t-Butyloxygruppen bevorzugt sind.

[0022] Als Vertreter für die Schutzgruppen PG sind Alkyl- und/oder Aryl-substituiertes Silyl, C_1-C_{20}-Alkyl, C_4-C_7-Cycloalkyl, das im Ring zusätzlich ein Sauerstoffatom enthalten kann, Aryl, C_7-C_{20}-Aralkyl, C_1-C_{20}-Acyl sowie Aroyl zu nennen.

[0023] Als Alkyl-, Silyl- und Acylreste für die Schutzgruppen PG kommen die dem Fachmann bekannten Reste in Betracht. Bevorzugt sind aus den entsprechenden Alkyl- und Silylethern)eicht abspaltbare Alkyl- bzw. Silylreste, wie beispielsweise der Methoxymethyl-, Methoxyethyl, Ethoxyethyl-, Tetrahydropyranyl-, Tetrahydrofuranyl-, Trimethylsilyl-, Triethylsilyl-, tert.-Butyldimethylsilyl-, tert.-Butyldiphenylsilyl-, Tribenzylsilyl-, Trüsopropylsilyl-, Benzyl, para-Nitrobenzyl-, para-Methoxybenzyl-Rest sowie Alkylsulfonyl- und Arylsulfonylreste. Als Acylreste kommen z. B. Formyl, Acetyl, Propionyl, Isopropionyl, Pivalyl-, Butyryl oder Benzoyl, die mit Amino- und/oder Hydroxygruppen substituiert sein können, in Frage.

[0024] Als Aminoschutzgruppen kommen die dem Fachmann bekannten Reste in Betracht. Beispielsweise genannt seien die Alloc-, Boc-, Z-, Benzyl, f-Moc-, Troc-, Stabase- oder Benzostabase-Gruppe.

[0025] Die Acylgruppen PG können 1 bis 20 Kohlenstoffatome enthalten, wobei Formyl-, Acetyl-, Propionyl-, Isopropionyl und Pivalylgruppen bevorzugt sind.

[0026] Der Index m in der aus R^{1a} und R^{1b} gebildeten Alkylengruppe steht vorzugsweise für 1, 2, 3 oder 4.

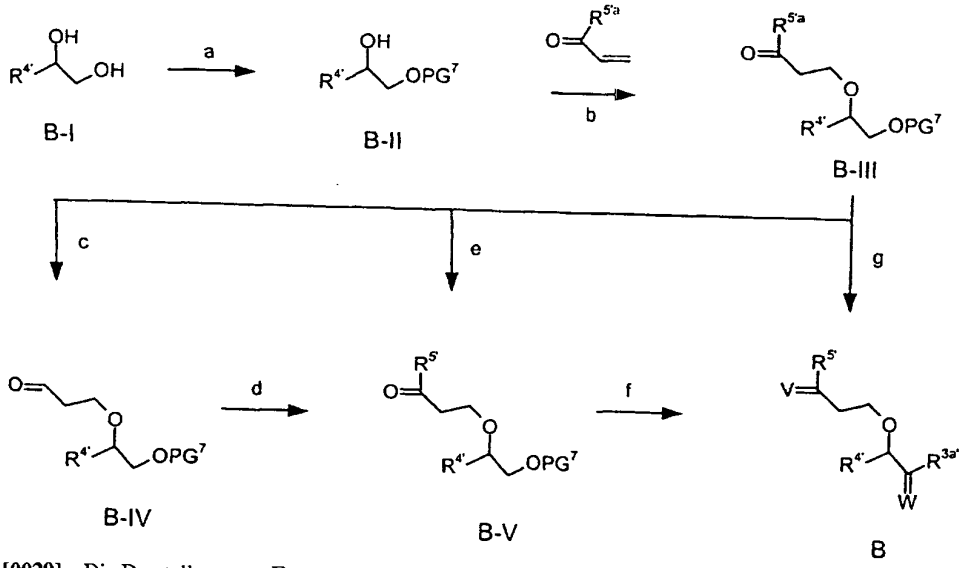
[0027] Die für R^{21}, R^{22}, V, W und X mögliche C_2-C_{10}-Alkylen-α,ω-dioxygruppe ist vorzugsweise eine Ethylenketal- oder Neopentylketalgruppe.

Darstellung der Teilfragmente A

[0028] Die Teilfragmente (Synthesebausteine) der allgemeinen Formel A-1 und A-2 lassen sich wie in DE 197 51 200.3, DE 199 07 480.1, DE 19 92 10 861.1 und WO 99/07692 herstellen.

Darstellung der Teilfragmente B

Schema 1



[0029] Die Darstellung von Fragmenten des Typs B, in denen $R^{3a'}$, $R^{4'}$, $R^{5'}$, V und W alle bereits genannten Bedeutungen haben können, ist in Schema 1 gezeigt. Die Synthese kann sowohl ausgehend von enantiomerenreien Verbindungen B-I als auch racemisch durchgeführt werden.

Schritt a (B-I ⇒ B-II)

[0030] Verbindungen des Typs B-I sind z. T. käuflich. In diesen Fällen wird nach dem Fachmann bekannten Verfahren die primäre Alkoholfunktion selektiv geschützt. Prinzipiell kommen alle z. B. für PG^5 genannten Schutzgruppen in Frage. Besonders bevorzugt ist z. B. die Tetrahydropyranylschutzgruppe. Für nicht käufliche Verbindungen des Typs B-I wird der Rest $R^{4'}$ nach den dem Fachmann bekannten Verfahren, z. B. durch nukleophile Substitution an entsprechende Aldehyde hergestellt.

Schritt b (B-II ⇒ B-III)

[0031] Durch 1,4-Addition von Verbindungen des Typs B-II an α,β-ungesättigte Carbonylverbindungen werden Ver-

bindungen des Typs B-III erhalten. $R^{5'a}$ kann hierbei alle bereits für $R^{5'}$ genannten Bedeutungen haben und zusätzlich gleich O-Alkyl sein.

Schritt c (B-III ⇒ B-IV)

[0032] Für Verbindungen des Typs B-III, in denen $R^{5'a}$ die Bedeutung O-Alkyl hat, kann zum Aldehyd B-IV reduziert werden. Die Überführung in den Aldehyd erfolgt entweder direkt z. B. durch Reduktion mit Diisobutylaluminiumhydrid bei tiefen Temperaturen (unter –40°C) oder aber zweistufig durch Reduktion zum Alkohol und anschließende Oxidation. Hierfür kommen dem Fachmann bekannte Verfahren zur Anwendung. Für die Reduktion werden z. B. komplexe Hydride wie Lithiumaluminiumhydrid verwendet. Die Oxidation kann z. B. nach den zur Darstellung von A-III beschriebenen Verfahren erfolgen.

Schritt d (B-IV ⇒ B-V)

[0033] Durch nucleophile Addition von metallorganischen Verbindungen der theoretischen Formel $M\text{-}R^{5'}$, worin M für Indium, ein Alkalimetall, vorzugsweise Lithium oder ein zweiwertiges Metall MX, worin X ein Halogen repräsentiert und der Rest $R^{5'}$ die oben genannten Bedeutungen aufweist. Als zweiwertiges Metall ist bevorzugt Magnesium und Zink, als Halogen X ist bevorzugt Chlor, Brom und Iod.

Schritt e (B-III ⇒ B-V)

[0034] Für Verbindungen, in denen $R^{5'a}$ für O-Alkyl steht, kann man auch direkt durch nucleophile Addition zu Verbindungen des Typs B-V gelangen. Hierfür kommen dem Fachmann bekannte Methoden zum Einsatz, wie z. B. die Verwendung von Dialkylkupferlithium-Verbindungen.

Schritt f (B-V ⇒ B)

[0035] Die Überführung von B-V in Teilfragmente der allgemeinen Formel B erfolgt analog zu den in WO 99/07692 beschriebenen Verfahren.

Schritt g (B-III ⇒ B)

[0036] Für Verbindungen, in denen $R^{5'a}$ nicht O-Alkyl bedeutet, kann Verbindung B-III ebenfalls analog WO 99/07692 in Teilfragmente des Typs B überführt werden.

Darstellung der Teilfragmente C

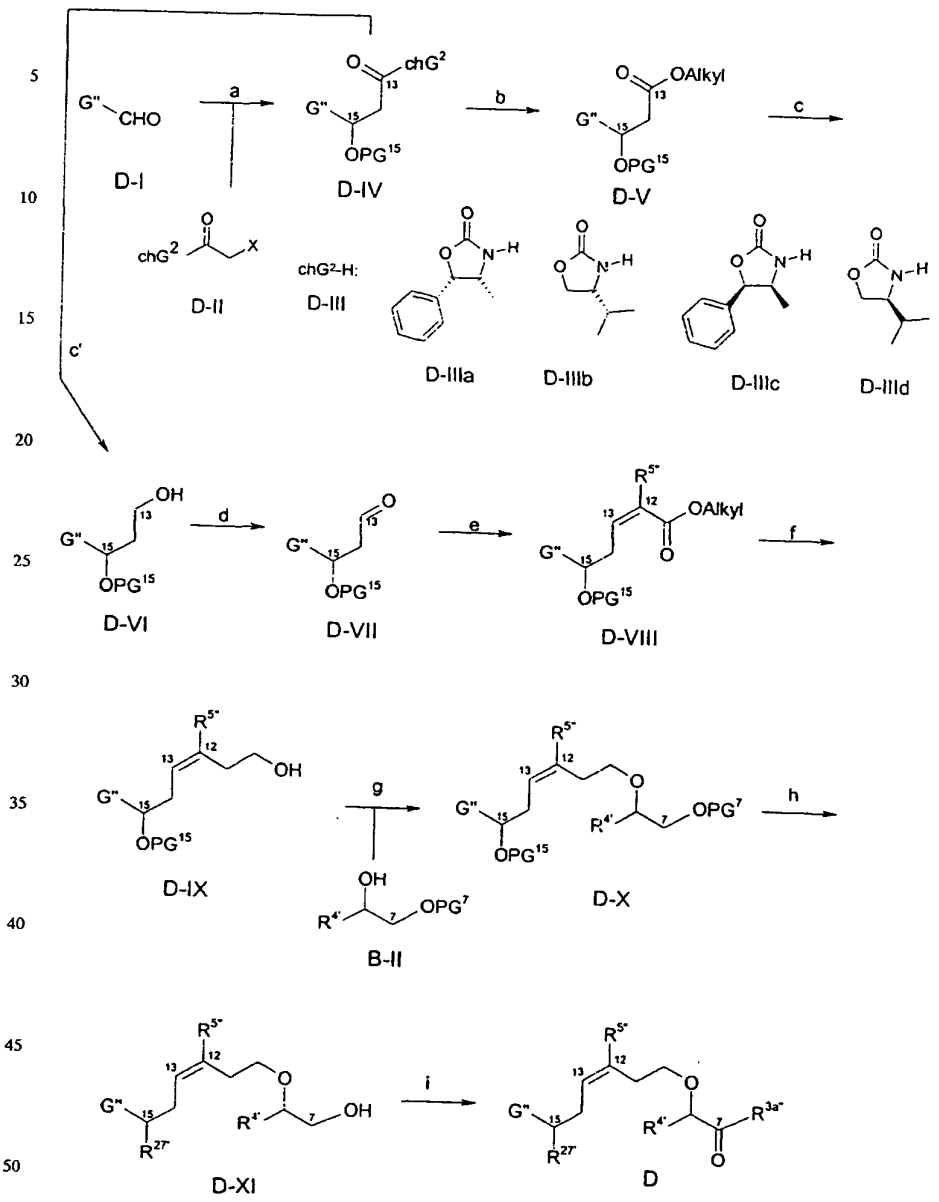
[0037] Die Teilfragmente (Synthesebausteine) der allgemeinen Formel C lassen sich wie in DE 197 51 200.3, DE 199 07 480.1 und WO 99/07692 herstellen.

[0038] Darstellung der Teilfragmente ABC und deren Zyklisierung zu I erfolgt ebenfalls analog wie in WO 99/07692 für zahlreiche Epothilon-Derivate beschrieben ist, WO 99/07692 belegt schon die allgemeine Anwendbarkeit des nachfolgend für die erfindungsgemäßen Verbindungen beschriebenen Syntheseprinzips. Außerdem gehen aus WO 99/07692 zahlreiche Synthesebausteine der allgemeinen Formeln A, B und C hervor, mit denen sich weitere der hier beanspruchten Verbindungen der allgemeinen Formel I erhalten lassen. Synthesebausteine der allgemeinen Formel C, in denen als R^{12} ein Halogenatom, insbesondere ein Fluor-, Chlor- oder Bromatom, vorhanden ist, sind Gegenstand der DE 199 07 480.1 und PCT/EP00/01333.

Darstellung der Teilfragmente D

[0039] Die Synthese der Teilfragmente D ist im folgenden Schema 2 ausgehend von den Aldehyden der allgemeinen Formel D-I beschrieben.

Schema 2



Schritt a (D-I ⇒ D-IV)

[0040] Die Verbindung D-I wird mit dem Enolat einer Carbonylverbindung der allgemeinen Formel D-II, worin X ein Wasserstoff und chG^2 eine chirale Hilfsgruppe sein kann, nach den, dem Fachmann bekannten Methoden alkyliert. Das Enolat wird durch Einwirkung starker Basen wie z. B. Lithiumdiisopropylamid, Lithiumhexamethyldisilazan bei niedrigen Temperaturen hergestellt. Eine weitere Möglichkeit besteht in einer Art Reformatzsky-Reaktion bei der die Verbindung der allgemeinen Formel D-II mit X = Halogen, vorzugsweise Chlor oder Brom, mit $CrCl_2$ in ein metallorganisches Reagenz überführt wird, welches dann mit dem Aldehyd D-I zu D-IV reagiert. Als chirale Hilfsgruppe chG^2-H (D-III) eignen sich chirale, optisch rein herstellbare und wohlfeile Alkohole wie z. B. Pulegol, 2-Phenylcyclohexanol, 2-Hydroxy-1,2,2-triphenylethanol, 8-Phenylmenthol oder optisch rein herstellbare und wohlfeile, reaktive NH-Gruppen enthaltende Verbindungen wie z. B. Amine, Aminosäuren, Lactame oder Oxazolidinone. Bevorzugt sind Oxazolidinone, besonders bevorzugt die Verbindungen der Formeln D-IIIa bis D-IIId. Durch die Wahl des jeweiligen Antipoden wird die absolute Stereochemie am α-Carbonylkohlenstoff der Verbindung der allgemeinen Formel D-IV festgelegt. Auf diesem Wege lassen sich die Verbindungen der allgemeinen Formeln D-IV bis D-XV bzw. deren jeweilige Enantiomere ent-D-IV bis ent-D-XV enantiomerenrein erhalten. Wird als chG^2-H (D-III) ein achiraler Alkohol wie z. B. Ethanol eingesetzt, so erhält man die racemischen Verbindungen rac-D-IV bis rac-D-XV.

[0041] Anschließend wird die freie Hydroxylgruppe in B-IV nach den, dem Fachmann bekannten Methoden geschützt. Als Schutzgruppen PG15 kommen die, dem Fachmann bekannten Schutzgruppen, wie sie schon vorstehend für PG5 (A-I → A-II) genannt wurden, in Frage.

[0042] Bevorzugt sind Silizium haltige Schutzgruppen, die unter sauren Reaktionsbedingungen oder Anwendung von Fluorid gespalten werden können, wie z. B. der Trimethylsilyl-, Triethylsilyl-, tert.-Butyldimethylsilyl-, tert.-Butyldiphenyisilyl-, Tribenzylsilyl-, Triisopropylsilyl-Rest.

[0043] Besonders bevorzugt ist der tert.-Butyldiphenylsilyl- und tert.-Butyldimethylsilyl Rest.

Schritt b (D-IV → D-V)

[0044] Repräsentiert die Gruppe chG^2 eine der unter Schritt a erwähnten chiralen Hilfsgruppen, so wird diese durch Umesterung von D-IV in einen Alkylester der allgemeinen Formel D-V wiedergewonnen. Die Umesterung erfolgt nach den, dem Fachmann bekannten Methoden. Bevorzugt ist die Umesterung mit einfachen Alkoholen wie z. B. Methanol oder Ethanol in Gegenwart entsprechender Titan(IV)alkoholate.

Schritt c (D-V → D-VI)

[0045] Der Ester in D-V wird zum Alkohol D-VI reduziert. Als Reduktionsmittel eignen sich die, dem Fachmann bekannten Reduktionsmittel wie z. B. Aluminiumhydride wie z. B. Lithiumaluminiumhydrid oder Diisobutylaluminiumhydrid. Die Reaktion erfolgt in einem inerten Lösungsmittel wie z. B. Diethylether, Tetrahydrofuran, Toluol.

Schritt c' (D-IV → D-VI)

[0046] Alternativ zu den Schritten b) und c) kann die Carbonylgruppe in D-IV nach den unter Schritt c) genannten Bedingungen direkt zu den Alkoholen der allgemeinen Formel D-VI reduziert werden. Auch hier kann die chirale Hilfskomponente chG^2-H wiedergewonnen werden.

Schritt d (D-VI → D-VII)

[0047] Die Oxidation des primären Alkohols in D-VI zum Aldehyd der allgemeinen Formel D-VII erfolgt nach den, dem Fachmann bekannten Verfahren. Beispielsweise genannt sei die Oxidation mit Pyridiniumchlorochromat, Pyridiniumdichromat, Chromtrioxid-Pyridin-Komplex, die Oxidation nach Swern oder verwandter Methoden z. B. unter Verwendung von SO_3-Pyridin-Komplex oder Oxalylchforid in Dimethylsulfoxid, die Verwendung des Dess-Martin-Periodinans, die Verwendung von Stickstoffoxiden wie z. B. N-Methyl-morpholino-N-oxid in Gegenwart geeigneter Katalysatoren wie z. B. Tetrapropylammoniumperruthenat in inerten Lösungsmitteln. Bevorzugt ist die Oxidation nach Swern, SO_3-Pyridin-Komplex sowie mit N-Methyl-morpholino-N-oxid unter Verwendung von Tetrapropylammoniumperruthenat.

Schritt e (D-VII → D-VIII)

[0048] Die ungesättigten Ester der allgemeinen Formel D-VIII werden durch die dem Fachmann bekannten Verfahren hergestellt. Hierzu eignen sich Methoden wie z. B. die Wittig- oder Wittig/Horner-Reaktion, oder auch die Peterson-Olefinierung. Bevorzugt ist die Wittig/Horner-Reaktion unter Verwendung von Phosphonaten des Typs $AlkylOOC\text{-}CHR^{5''}\text{-}P(O)(OAlkyl')_2$, wobei Alkyl und Alkyl' gleich oder verschieden sein können und vorzugsweise Methyl, Ethyl, i-Propyl oder Trifluorethyl bedeuten und R5' die bereits genannte Bedeutung hat, mit Basen wie z. B. Kaliumcarbonat, Natriumhydrid, n-Butyllithium, Kalium-tert.-butanolat, Natriumethanolat, Lithiumhexamethyldisilazan, Natriumhexamethyldisilazan, Kaliumhexamethyldisilazan und gegebenenfalls mit Zusätzen von beispielsweise Kronenethern, DMPU oder HMPA, in Lösungsmittel wie Methanol, Tetrahydrofuran, Dimethylformamid, Diethylether, bevorzugt ist die Kombination von Kaliumcarbonat in Methanol, Natriumhydrid in Dimethylformamid oder Tetrahydrofuran und Kaliumhexamethyldisilazan mit 18-Krone-6 in Tetrahydrofuran.

[0049] Die erhaltenen E/Z-Diastereomeren können beispielsweise auf dieser oder der nächsten Stufe getrennt werden und können einzeln für sich in die entsprechenden E- bzw. Z-Olefinendprodukte überführt werden. In dem Formelschema ist der übersichtlichkeithalber nur die E-Form dargestellt. Alle folgende Schritte gelten jedoch auch für das entsprechende Z-Isomer.

Schritt f (D-VIII → D-IX)

[0050] Verbindungen des Typs D-VIII werden durch C_1-Verlängerung in Verbindungen des Typs D-IX überführt. Diese C_1-Verlängerung erfolgt nach mehrstufigen Verfahren. Beispielsweise kann die Esterfunktion in D-VIII zu einem primären Alkohol reduziert werden. Als Reduktionsmittel eignen sich die, dem Fachmann bekannten Reduktionsmittel wie z. B. Aluminiumhydride wie z. B. Lithiumaluminiumhydrid oder Diisobutylaluminium-hydrid. Die Reaktion erfolgt in einem inerten Lösungsmittel wie z. B. Diethylether, Tetrahydrofuran, Toluol. Der primäre Alkohol kann dann in eine Fluchtgruppe, wie z. B. ein Halogenid oder eine OSO_2-Alkyl-, O-SO_2-Aryl- oder OSO_2-Aralkylgruppe überführt werden. Die Einführung des späteren C-14 kann dann z. B. mittels Substitution durch Cyanid unter Verwendung von NaCN oder KCN erfolgen. Das gebildete Nitril wird anschließend durch Reduktion mit z. B. Diisobutylaluminium-hydrid und saure Spaltung des primär gebildeten Imins in einen Aldehyd überführt, der dann z. B. mit Lithiumaluminiumhydrid, Natriumborhydrid oder Diisobutylaluminium-hydrid in den primären Alkohol des Typs D-IX überführt wird.

Schritt g (D-IX + B-II → D-X)

[0051] Die Darstellung von Verbindungen des Typs D-X erfolgt dann durch Verknüpfung von D-IX mit bereits beschriebenen Verbindungen des Typs B-II. Diese läßt sich z. B. unter Verwendung von Triphenylphosphin und Azodiestern wie beispielsweise Azodicarbonsäurediethylester durchführen. Alternativ hierzu kann auch eine der beiden Hydroxyfunktionen (in Baustein D-IX oder B-II) in ein Halogenid oder eine OSO_2Alkyl, OSO_2Aryl oder OSO_2Aralkyl-Gruppe überführt uverden. Vorzugsweise wird die Fluchtgruppe an der primären Alkoholfunktion in Baustein D-IX gebildet. Zur Verknüpfung beider Bausteine wird dann die freie Hydroxylgruppe in dem jeweils anderen Baustein, vorzugsweise B-II, mit geeigneten Basen wie beispielsweise Natriumhydrid, n-Buthyllithium, 4-Dimethylaminopyridin, Hünig-Base, Alkylihexamethyldisilazanen deprotoniert und durch nucleophile Substitution in Verbindungen des Typs D-X überführt.

Schritt h (D-X → D-XI)

[0052] Für den Fall, daß $R^{27'} = OPG^{27}$ ist wird die Schutzgruppe PG^7 nun nach den, dem Fachmann bekannten Verfahren gespalten. Handelt es sich um eine sauer spaltbare Schutzgruppe, so eignen sich für die Spaltung verdünnte Mineralsäuren in wässrigalkoholischen Lösungen, die Verwendung von katalytischen Mengen Säuren wie z. B. para-Toluolsulfonsäure, para-Toluolsulfonsäure-pyridiniumsalz, Camphersulfonsäure in alkoholischen Lösungen, vorzugsweise in Ethanol oder Isopropanol.

[0053] Für den Fall, daß A in den Verbindungen der Formel I eine NR^{17}-Gruppe ist, wird vor der Abspaltung der Schutzgruppe PG^7 zuerst die Schutzgruppe PG^{27} selektiv nach den, dem Fachmann bekannten Methoden gespalten (s. hierzu auch weiter oben). Den so erhaltenen sekundären Alkohol überführt man mit einem Sulfonylchlorid oder einem Sulfonsäureanhydrid in ein Sulfonat und gegebenfalls anschließend in einer Finkelstein-Reaktion mit einem Alkalibromid oder -chlorid, oder durch Reaktion des sekundären Alkohols mit CBr_4 in Gegenwart von Triphenylphosphin bzw. Bis(diphenylphosphinoethan) in ein sekundäres Halogenid. Die so erhaltenen Halogenide oder Sulfonate können dann durch eine nucleophile Substitution mit z. B. Natriumazid in einem neutralen polaren Lösungsmittel wie beispielsweise Dimethylformamid oder Dimethylsulfoxid in ein entsprechendes Azid ($L' = N_3$) überführt werden. Danach würde sich die oben beschriebene Spaltung der Schutzgruppe PG^7 anschließen.

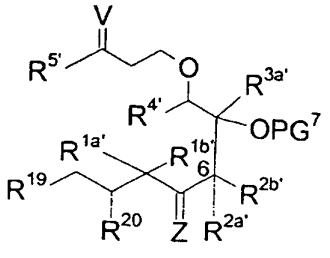
Schritt i (D-XI → D)

[0054] Die Oxidation des primären Alkohols in D-XI zum entsprechenden Aldehyd erfolgt nach den, dem Fachmann bekannten Verfahren. Beispielsweise genannt sei die Oxidation mit Pyridiniumchlorochromat, Pyridiniumdichromat, Chromtrioxid-Pyridin-Komplex, die Oxidation nach Swern oder verwandter Methoden z. B. unter Verwendung von SO_3-Pyridin-Komplex oder von Oxalylchlorid in Dimethylsulfoxid, die Verwendung des Dess-Martin-Periodinans, die Verwendung von Stickstoffoxiden wie z. B. N-Methyl-morpholino-N-oxid in Gegenwart geeigneter Katalysatoren wie z. B. Tetrapropylammoniumperruthenat in inerten Lösungsmitteln. Bevorzugt ist die Oxidation nach Swern sowie mit N-Methyl-morpholino-N-oxid unter Verwendung von Tetrapropylammoniumperruthenat.

[0055] Für den Fall das $R^{3a''} \neq H$ ist, kann jetzt nach den, dem Fachmann bekannten Methoden mit metallorganischen Verbindungen der allgemeinen Formel $M\text{-}R^{3a''}$, worin M für ein Alkalimetall, vorzugsweise Lithium oder ein zweiwertiges Metall MX, worin X ein Halogen repräsentiert und der Rest $R^{3a''}$ die oben genannte Bedeutung aufweist, der entsprechende sekundäre Alkohol hergestellt werden. Als zweiwertiges Metall ist bevorzugt Magnesium und Zink, als Halogen X ist bevorzugt Chlor, Brom und Iod.

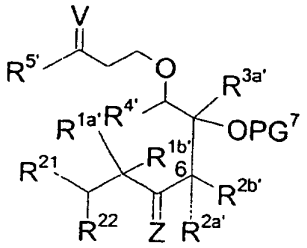
[0056] Der so erhaltene sekundäre Alkohol wird durch Oxidation in das Keton der allgemeinen Formel D mit $R3' \neq H$ nach den unter i) zu anfangs genannten Verfahren überführt. Bevorzugt ist die Oxidation mit N-Methyl-morpholino-N-oxid unter Verwendung von Tetrapropylammoniumperruthenat.

Teilfragmente der allgemeinen Formel AB



AB-1

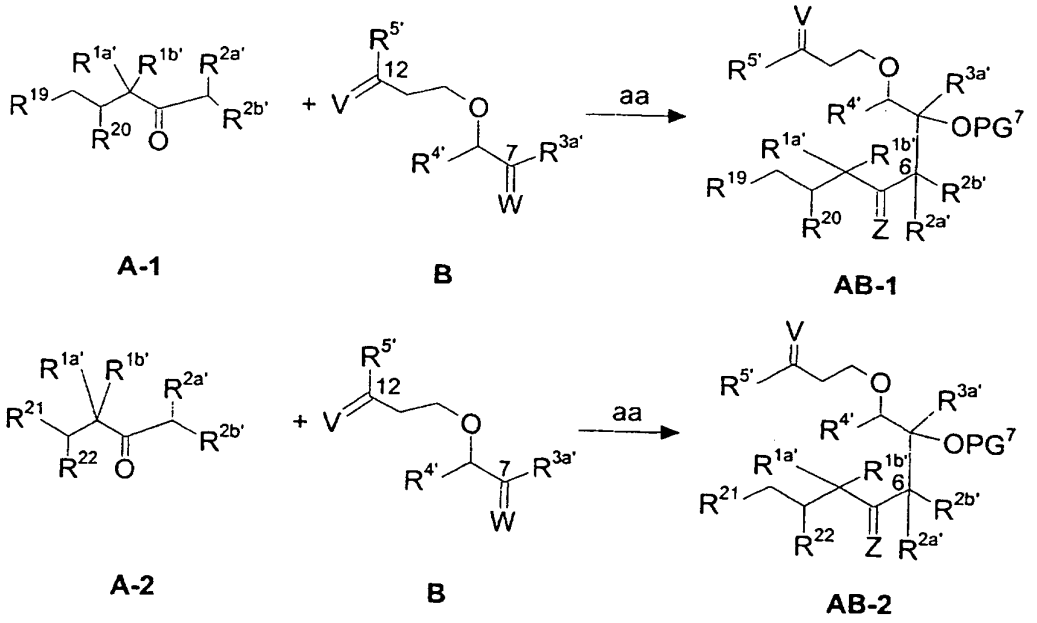
bzw.



AB-2

worin $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, $R^{3a'}$, $R^{4'}$, $R^{5'}$, R^{19}, R^{20}, R^{21}, R^{22}, V und Z die bereits genannten Bedeutungen haben und PG^7 ein Wasserstoffatom oder eine Schutzgruppe PG darstellt, werden aus den zuvor genannten Fragmenten A und B nach dem in Schema 3 gezeigten Verfahren erhalten.

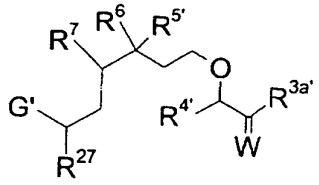
Schema 3



Schritt aa (A + B ⇒ AB)

[0057] Die Verbindung B, worin W die Bedeutung eines Sauerstoffatomes hat und eventuell vorhandene zusätzliche Carbonylgruppen geschützt sind, wird mit dem Enolat einer Carbonylverbindung der allgemeinen Formel A alkyliert. Das Enolat wird durch Einwirkung starker Basen wie z. B. Lithiumdiisopropylamid, Lithiumhexamethyldisilazan bei niedrigen Temperaturen hergestellt.

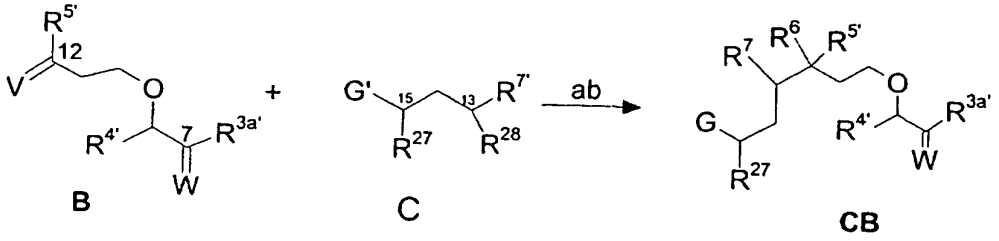
Teilfragmente der allgemeinen Formel BC



BC,

worin $R^{3a'}$, $R^{4'}$, $R^{5'}$, R^6, R^7, R^{27}, G und W die bereits genannten Bedeutungen haben, werden aus den zuvor beschriebenen Fragmenten B und C nach dem in Schema 4 gezeigten Verfahren erhalten.

Schema 4

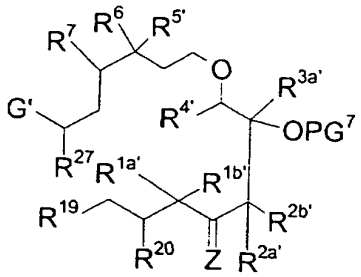


Schritt ab (B + C ⇒ BC)

[0058] Die Verbindung C, in der R^{28} die Bedeutung eines Wittigsalzes hat und eventuell vorhandene zusätzliche Carbonylgruppen geschützt sind, wird durch eine geeignete Base wie z. B. n-Butyllithium, Lithiumdiisopropylamaid, Kalium-tertbutanolat, Natrium- oder Lithium-hexamethyldisilazid deprotoniert und mit einer Verbindung B, worin V die

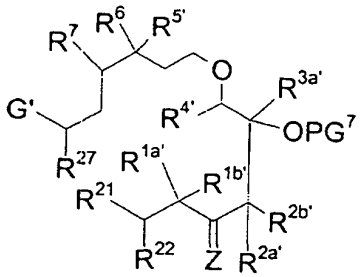
Bedeutung von Sauerstoff und W die Bedeutung zweier Alkoxygruppen OR^{25}, einer C_2-C_{10}-Alkylen-α,ω-dioxygruppe, die geradkettig oder verzweigt sein kann oder H/OR^{26} hat, umsetzt.

Teilfragmente der allgemeinen Formel ABC (AB + C)



ABC-1

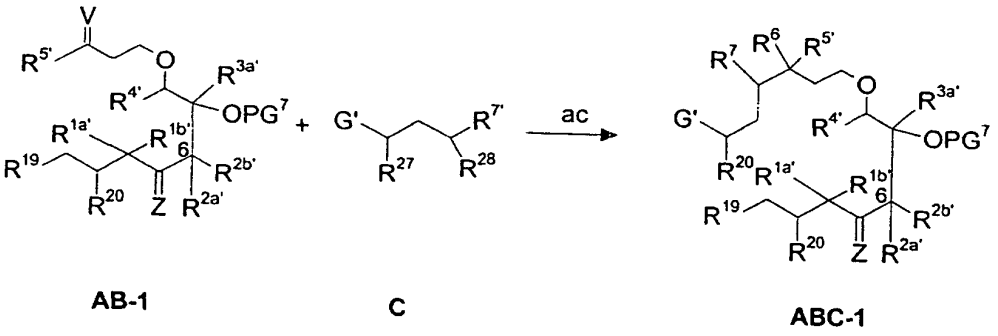
bzw.



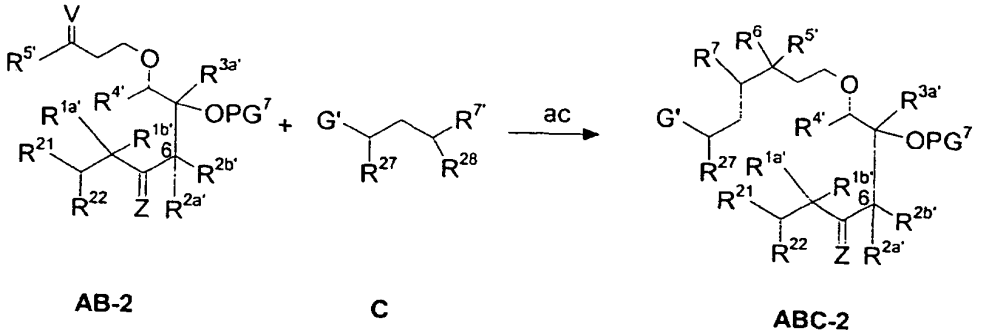
ABC-2,

worin $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, $R^{3a'}$, $R^{4'}$, $R^{5'}$, R^{6}, R^{7}, R^{19}, R^{20}, R^{21}, R^{22}, G' und Z die bereits genannten Bedeutungen haben und PG^7 ein Wasserstoffatom oder eine Schutzgruppe PG darstellt, werden aus den zuvor beschriebenen Fragmenten AB und C nach dem in Schema 5 und Schema 6 gezeigten Verfahren erhalten.

Schema 5



AB-1 **C** **ABC-1**

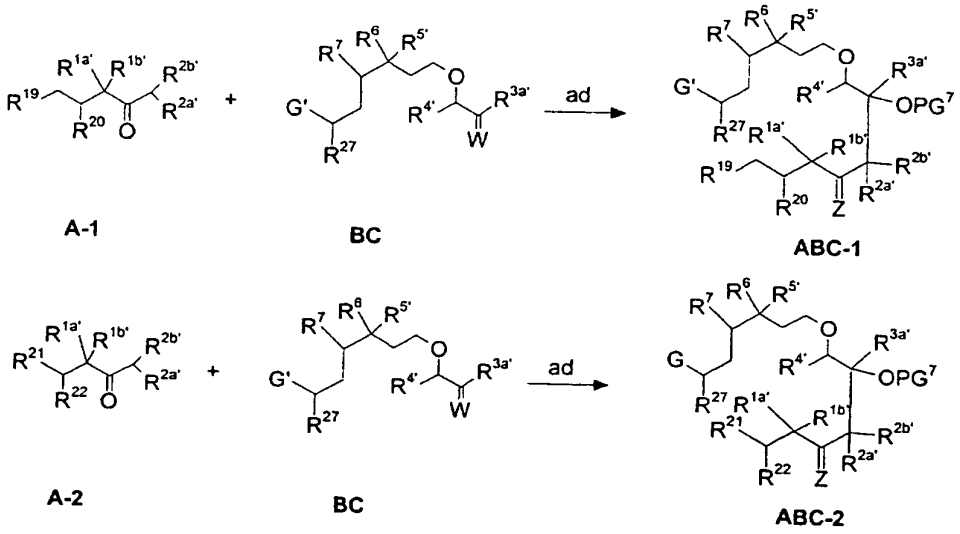


AB-2 **C** **ABC-2**

Schritt ac (AB + ⇒ ABC)

[0059] Die Verbindung C, in der R^{28} die Bedeutung eines Wittigsalzes hat und eventuell vorhandene zusätzliche Carbonylgruppen gegebenenfalls geschützt sind, wird durch eine geeignete Base wie z. B. n-Butyllithium, Lithiumdiisopropylamid, Kalium-tert.-butanolat, Natrium- oder Lithium-hexamethyldisilazid deprotoniert und mit einer Verbindung AB, worin V die Bedeutung eines Sauerstoffatomes hat, umgesetzt.

Schema 6

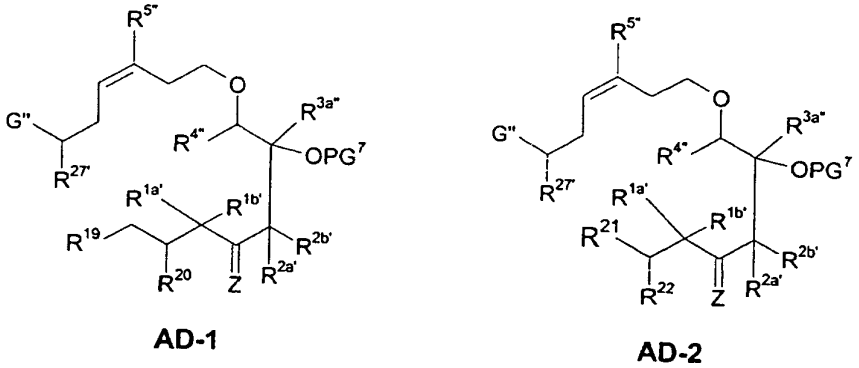


Schritt ad (A+BC ⇒ ABC)

[0060] Die Verbindung BC, worin W die Bedeutung eines Sauerstoffatomes hat und eventuell vorhandene zusätzliche Carbonylgruppen geschützt sind, wird mit dem Enolat einer Carbonylverbindung der allgemeinen Formel A alkyliert. Das Enolat wird durch Einwirkung starker Basen wie z. B. Lithiumdiisopropylamid, Lithiumhexamethyldisilazan bei niedrigen Temperaturen hergestellt.

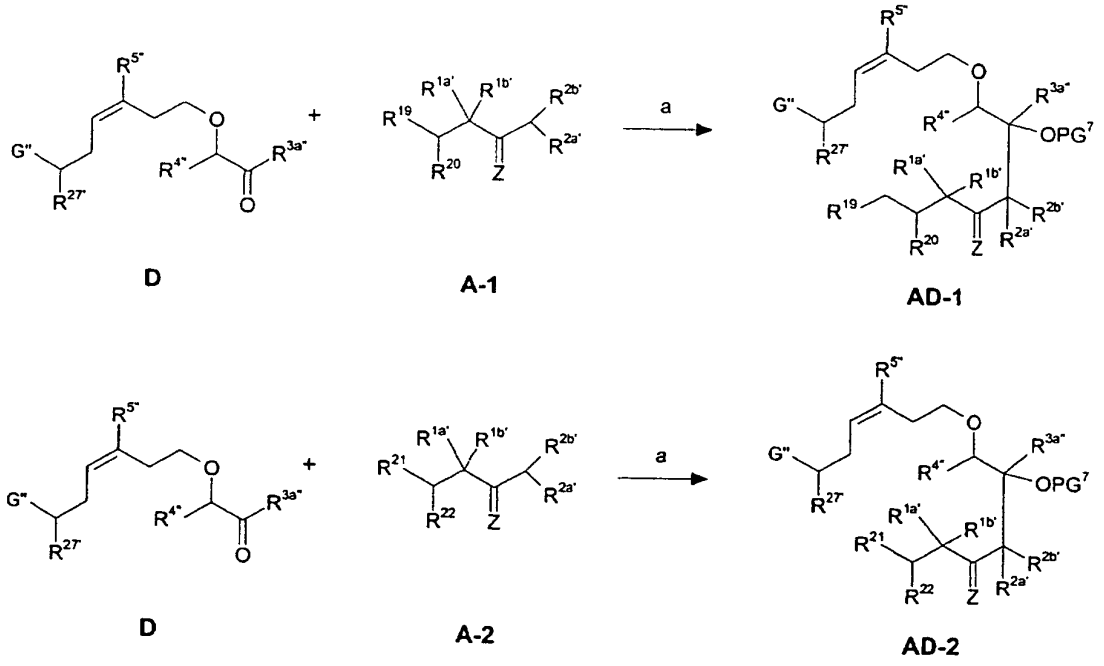
Darstellung der Teilfragmente AD

Teilfragmente der allgemeinen Formel AD



worin $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, $R^{3a'}$, $R^{4'}$, $R^{5''}$, R^{19}, R^{20}, $R^{27'}$, G" und Z die bereits genannten Bedeutungen haben, werden aus den zuvor beschriebenen Fragmenten A und D nach dem in Schema 7 gezeigten Verfahren erhalten.

Schema 7



Schritt a (A+ D ⇒ AD)

[0061] Die Verbindung D wird mit dem Enolat einer Carbonylverbindung der allgemeinen Formel A alkyliert. Das Enolat wird durch Einwirkung starker Basen wie z. B. Lithiumdiisopropylamid, Lithiumhexamethyldisilazan bei niedrigen Temperaturen hergestellt.

[0062] Die Überführung von den Fragmenten ABC bzw. AD in Verbindungen der allgemeinen Formel I erfolgt nach den im folgenden beschriebenen Verfahren. Der einzige Unterschied zwischen den Fragmenten ABC und AD besteht darin, daß in den Fragmenten ABC der Rest R^5 alle Bedeutungen von R^5 außer Halogen und Cyano heben kann, während in den Fragmenten AD $R^{5''}$ Halogen oder Cyano bedeutet.

Schritt ae (ABC-1 oder AD-1 ⇒ I)

[0063] Die Verbindungen ABC-1 oder AD-1, in denen R^{19} eine Carbonsäure CO_2H und R^{27} eine Hydroxylgruppe oder eine Aminogruppe darstellt, setzt man nach den, dem Fachmann bekannten Methoden für die Bildung großer Macrolide bzw. Marolactame zu Verbindungen der Formel I, in denen A-Y die Bedeutung einer O-(C = O)-Gruppe oder NR^{29}-C(C=O)-Gruppe besitzt, um. Beispielsweise bevorzugt für die Lactonbildung wird die in "Reagents for Organic Synthesis, Vol. 16, p 353" beschriebene Methode unter Verwendung von 2,4,6-Trichlorbenzoesäurechlorid und geeigneten Basen wie z. B. Triethylamin, 4-Dimethylaminopyridin, Natriumhydrid. Beispielsweise bevorzugt für die Lactambildung wird die Umsetzung der Aminosäure (R^{19} eine Carbonsäure CO_2H und R^{27} eine NHR^{29}-Gruppe) mit Diphenylphosphorylazid in Gegenwart einer Base.

Schritt af (ABC-1 oder AD-1 ⇒ I)

[0064] Die Verbindungen ABC-1 oder AD-1, in denen R^{19} eine Gruppe CH_2OH und R^{27} eine Hydroxylgruppe darstellt, lassen sich vorzugsweise unter Verwendung von Triphenylphosphin und Azodiestern wie beispielsweise Azodicarbonsäurediethylester zu Verbindungen der Formel I, in denen A-Y die Bedeutung einer O-CH_2-Gruppe hat, umsetzen.

[0065] Die Verbindungen ABC oder AD, in denen R^{19} eine Gruppe CH_2-Hal oder CH_2OSO_2Alkyl oder CH_2OSO_2Aryl oder CH_2OSO_2Aralkyl und R^{27} eine Hydroxylgruppe darstellt, lassen sich nach Deprotonierung mit geeigneten Basen wie beispielsweise Natriumhydrid, n-Buthyllithium, 4-Dimethylaminopyridin, Hünig-Base, Alkylihexamethyldisilazanen zu Verbindungen der Formel I, in denen A-Y die Bedeutung einer O-CH_2-Gruppe hat, zyklisieren.

Schritt ag (ABC-2 oder AD-2 ⇒ I)

[0066] Die Verbindungen ABC-2 oder AD-2, in denen R^{21} und R^{22} gemeinsam ein Sauerstoffatom und R^{27} eine $NR^{29}SO_2CH_3$-Gruppe darstellt, lassen sich durch Einwirkung starker Basen wie z. B. Lithiumdiisopropylamid, Lithiumhexamethyldisilazan bei niedrigen Temperaturen zum Sulfonamid I, in dem A-Y die Bedeutung einer $NR^{29}SO_2$-Gruppe hat, zyklisieren.

Schritt ah (ABC-2 oder AD-2 ⇒ I)

[0067] Die Verbindungen ABC-2 oder AD-2, in denen R^{21} und R^{22} gemeinsam ein Sauerstoffatom und R^{27} eine O-C(=O)CH_3-Gruppe darstellt, lassen sich durch Einwirkung starker Basen wie z. B. Lithiumdiisopropylamid, Alkalihexamethyldisilazan bei niedrigen Temperaturen zum Lacton I, in dem A-Y die Bedeutung einer O-C(=O)-Gruppe hat, zyklisieren.

Schritt ah (ABC-2 oder AD-2 ⇒ I)

[0068] Die Verbindungen ABC-2 oder AD-2, in denen R^{21} und R^{221} gemeinsam ein Sauerstoffatom und R^{27} eine $CH_2C(=O)CH_3$-Gruppe darstellt, lassen sich durch Einwirkung starker Basen wie z. B. Lithiumdiisopropylamid, Alkalihexamethyldisilazan bei niedrigen Temperaturen zum Lacton I, in dem A-Y die Bedeutung einer $CH_2C(=O)$-Gruppe hat, zyklisieren.

Einführung der Stickstoffunktion für R^{27}

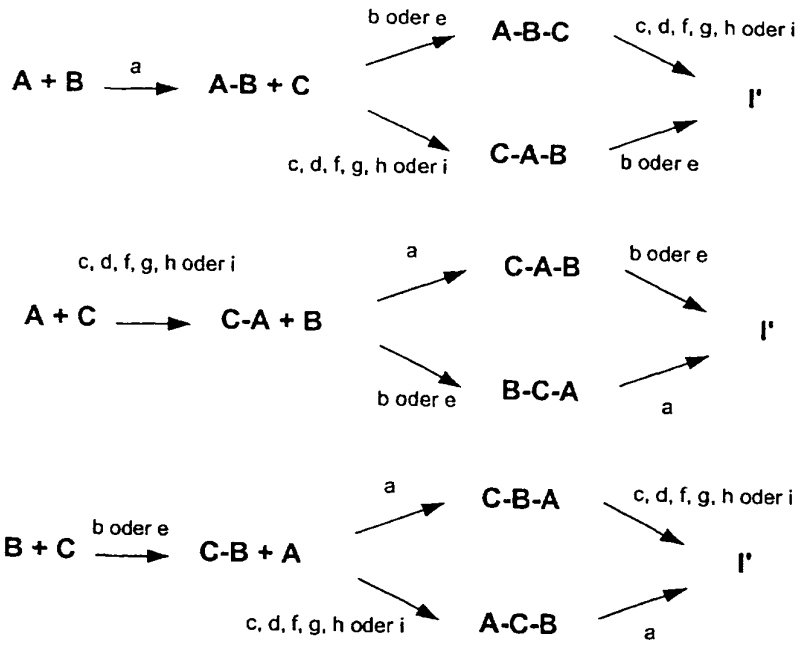
[0069] Die Aminogruppe NHR^{29} kann auf der Stufe des C-Fragmentes, des BC-Fragmentes oder des ABC-Fragmentes nach den, dem Fachmann bekannten Methoden eingeführt werden. Bevorzugt ist die Herstellung aus dem Azid (R^{27} = N_3), das nach den, dem Fachmann bekannten Methoden vorzugsweise unter Verwendung eines Phosphins wie beispielsweise Triphenylphosphin in Gegenwart von Wasser in das gegebenenfalls für den weiteren Reaktionsverlauf zu schützende Amin (R^{27} = NHR^{29}) überführt wird. Die Einführung des Azides kann unter Anwendung der Mitsunobu-Reaktion in Gegenwart von Metallaziden vorzugsweise Natrium- oder Zinkazid oder durch Substitution einer geeigneten Abgangsgruppe wie beispielsweise eines Chlor-, Brom- oder Iodatomes, einer Alkylsulfonyloxy-, einer perfluorierten Alkyisulfonyloxy-, einer Aryisulfonyloxy- oder einer Aralkylsulfonyloxy-Gruppe durch Azide erfolgen.

[0070] Die flexible Funktionalisierung der beschriebenen Bausteine A, B und C gewährleistet auch eine von dem oben beschriebenen Verfahren abweichende Verknüpfungsreihenfolge, die zu den Bausteinen ABC führt. Diese Verfahren sind in der folgenden Tabelle zusammengestellt:

Verknüpfungs-möglichkeiten	Verknüpfungs-methoden a bis e	Voraussetzungen
A + B ⇒ A-B	a: Aldol (siehe Schema 3)	Z = W = Sauerstoff
B + C ⇒ B-C	b: Wittig (analog Schema 4)	U = Sauerstoff und R^{28} = Wittigsalz, Phosphinoxid oder Phosphonat
	e: McMurry	U = V = Sauerstoff
A + C ⇒ A-C	c: Veresterung (z. B. 2,4,6-Trichlorbenzoylchlorid und 4-Dimethylamino-pyridin)	R^{19} = CO_2R^{19b} oder COHal und R^{27} = Hydroxyl
	d: Veretherung (z.B. nach Mitsunobu)	R^{19} = CH_2OH und R^{27} = Hydroxyl oder OSO_2-Alkyl oder OSO_2-Aryl oder OSO_2-Aralkyl
	f: Amidbildung (z.B. mit $(PhO)_2P(O)N_3$) in Gegenwart einer Base in einem inerten Lösungsmittel.	R^{19} = CO_2R^{19b} oder COHal und R^{27}= NHR^{29}
	g: Ketonbildung durch Aldolreaktion mit einer starken Base.	R^{27}= $CH_2C(=O)CH_3$ und R^{21}, R^{22}= Sauerstoff
	h: Sulfonamidbildung in Gegenwart einer starken Base.	R^{27}= $NR^{29}SO_2CH_3$ und R^{21}, R^{22}= Sauerstoff
	i: Amidbildung in Gegenwart einer starken Base.	R^{27}= $NR^{29}C(=O)CH_3$ und R^{21}, R^{22}= Sauerstoff

[0071] Nach diesen Verfahren lassen sich die Bausteine A, B und C, wie in Schema 10 angegeben, verknüpfen:

Schema 10



[0072] Freie Hydroxylgruppen in I, A, B, C, AB, BC, ABC können durch Veretherung oder Veresterung, freie Carbonylgruppen durch Ketalisierung, Enoletherbildung oder Reduktion weiter funktionell abgewandelt sein.

[0073] Die Erfindung betrifft alle Stereoisomeren dieser Verbindungen und auch deren Gemische.

[0074] Die Erfindung betrifft weiterhin alle Prodrugformulierungen dieser Verbindungen, d. h. alle Verbindungen, die in vivo eine bioaktive Wirkstoffkomponente der allgemeinen Formel I freisetzen.

Biologische Wirkungen und Anwendungsbereiche der neuen Derivate

[0075] Die neuen Verbindungen der Formel I sind wertvolle Pharmaka. Sie interagieren mit Tubulin, indem sie gebildete Mikrotubuli stabilisieren und sind somit in der Lage, die Zellteilung phasenspezifisch zu beeinflussen. Dies betrifft vor allem schnell wachsende, neoplastische Zellen, deren Wachstum durch interzelluläre Regelmechnismen weitgehend unbeeinflußt ist. Wirkstoffe dieser Art sind prinzipiell geeignet zur Behandlung maligner Tumoren. Als Anwendungsbereich seien beispielweise genannt die Therapie von Ovarial-, Magen-, Colon-, Adeno-, Brust-, Lungen-, Kopf- und Nakken-Karzinomen, dem malignen Melanom, der akuten lymphozytären und myelocytären Leukämie. Die erfindungsgemäßen Verbindungen eignen sich aufgrund ihrer Eigenschaften prinzipiell zur Anti-Angiogenese-Therapie sowie zur Behandlung chronischer entzündlicher Erkrankungen wie beispielsweise der Psoriasis, der multiplen Sklerose oder der Arthritis. Zur Vermeidung unkontrollierter Zellwucherungen an sowie der besseren Verträglichkeit von medizinischen Implantaten lassen sie sich prinzipiell in die hierfür verwendeten polymeren Materialien auf- bzw. einbringen. Die erfindungsgemäßen Verbindungen können alleine oder zur Erzielung additiver oder synergistischer Wirkungen in Kombination mit weiteren in der Tumortherapie anwendbaren Prinzipien und Substanzklassen verwendet werden.

[0076] Als Beispiele seien genannt die Kombination mit

- Platinkomplexen wie z. B. Cisplatin, Carboplatin,
- interkalierenden Substanzen z. B. aus der Klasse der Anthracycline wie z. B. Doxorubicin oder aus der Klasse der Antrapyrazole wie z. B. CI-941,
- mit Tubulin interagierenden Substanzen z. B. aus der Klasse der Vinka-Alkaloide wie z. B. Vincristin, Vinblastin oder aus der Klasse der Taxane wie z. B. Taxol, Taxotere oder aus der Klasse der Makrolide wie z. B. Rhizoxin oder andere Verbindungen wie z. B. Colchicin, Combretastatin A-4, Discodermolid und seine Analoga,
- DNA Topoisomeraseinhibitoren wie z. B. Camptothecin, Etoposid, Topotecan, Teniposid,
- Folat- oder Pyrimidin-Antimetaboliten wie z. B. Lometrexol, Gemcitubin,
- DNA alkylierenden Verbindungen wie z. B. Adozelesin, Dystamycin A,
- Inhibitoren von Wachstumsfaktoren (z. B. von PDGF, EGF, TGFb, EGF) wie z. B. Somatostatin, Suramin, Bombesin-Antagonisten,
- Inhibitoren der Protein Tyrosin Kinase oder der Protein Kinasen A oder C wie z. B. Erbstatin, Genistein, Staurosporin, Ilmofosin, 8-CI-cAMP,
- Antihormonen aus der Klasse der Antigestagene wie z. B. Mifepriston, Onapriston oder aus der Klasse der Antiöstrogene wie z. B. Tamoxifen oder aus der Klasse der Antiandrogene wie z. B. Cyproteronacetat,
- Metastasen inhibierenden Verbindungen z. B. aus der Klasse der Eicosanoide wie z. B. PGI_2, PGE_1, 6-Oxo-PGE_1 sowie deren stabiler Derivate (z. B. Iloprost, Cicaprost, Misoprostol).
- Inhibitoren onkogener RAS-Proteine, welche die mitotische Signaltransduktion beeinflussen wie beispielsweise

Inhibitoren der Farnesyl-Protein-Transferase,
- natürlichen oder künstlich erzeugten Antikörpern, die gegen Faktoren bzw. deren Rezeptoren, die das Tumorwachstum fördern, gerichtet sind wie beispielsweise der erbB2-Antikörper.

[0077] Die Erfindung betrifft auch Arzneimittel auf Basis der pharmazeutisch verträglichen, d. h. in den verwendeten Dosen nicht toxischen Verbindungen der allgemeinen Formel I, gegebenenfalls zusammen mit den üblichen Hilfs- und Trägerstoffen.

[0078] Die erfindungsgemäßen Verbindungen können mit Liposomen verkapselt oder in ein α-, β- oder γ-Cyclodextrinclathrat eingeschlossen sein.

[0079] Die erfindungsgemäßen Verbindungen können nach an sich bekannten Methoden der Galenik zu pharmazeutischen Präparaten für die enterale, percutane, parenterale oder lokale Applikation verarbeitet werden. Sie können in Form von Tabletten, Dragees, Gelkapseln, Granulaten, Suppositorien, Implantaten, injizierbaren sterilen wäßrigen oder öligen Lösungen, Suspensionen oder Emulsionen, Salben, Cremes und Gelen verabreicht werden.

[0080] Der oder die Wirkstoffe können dabei mit den in der Galenik üblichen Hilfsstoffen wie z. B. Gummiarabikum, Talk, Stärke, Mannit, Methylcellulose, Laktose, Tensiden wie Tweens oder Myrj, Magnesiumstearat, wäßrigen oder nicht wäßrigen Trägern, Paraffinderivaten, Netz-, Dispergier-, Emulgier-, Konservierungsmitteln und Aromastoffen zur Geschmackskorrektur (z. B. etherischen Ölen) gemischt werden.

[0081] Die Erfindung betrifft somit auch pharmazeutische Zusammensetzungen, die als Wirkstoff zumindest eine erfindungsgemäße Verbindung enthalten. Eine Dosiseinheit enthält etwa 0,1–100 mg Wirkstoff(e). Die Dosierung der erfindungsgemäßen Verbindungen liegt beim Menschen bei etwa 0,1–1000 mg pro Tag.

[0082] Die nachfolgenden Beispiele dienen der näheren Erläuterung der Erfindung, ohne sie darauf einschränken zu wollen:

Beispiel 1

4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethylcyclohexadec-13-en-2,6-dion

Beispiel 1a

(R)-1-(Tetrahydro-2H-pyran-2-yl(oxy))-propan-2-ol

[0083] Eine Lösung von 5 g (65,70 mmol) R-1,2-Propandiol, 6,15 ml (68 mmol) 3,4-Dihydro-2H-pyran und 0,2 g p-Toluolsulfonsäure-Pyridiniumsalz in 100 ml Dichlormethan wird 20 Stunden bei 25°C gerührt. Anschließend wird durch Zugabe von Triethylamin neutraliert und dann die Reaktionslösung im Vakuum eingegengt. Nach Säulenchromatographie an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan werden 7,08 g (44,18 mmol; 67%) 1a erhalten.
^{1}H-NMR ($CDCl_3$): δ = 1,13 (3H), 1,48–1,59 (4H), 1,70–1,90 (2H), 3,40–4,00 (5H) 4,55 (1H) ppm.

Beispiel 1 b

(5R)-5-Methyl-4-oxa-6-(tetrahydro-2H-pyran-2-yl(oxy))hexansäureethylester

[0084] Eine Lösung aus 7,08 g (44,18 mmol) der unter 1a beschriebenen Verbindung, 95 ml (877 mmol) Acrylsäureethylester, 3,5 ml wäßrige Tetrabutylammoniumhydroxidlösung (10%1g), 180 ml 50%ige wäßrige Natriumhydroxidlösung in 300 ml Toluol wird 2 Stunden bei 25°C gerührt. Danach wird die Lösung auf Eiswasser gegossen. Man extrahiert mit Ethylacetat, wäscht die organische Phase mit gesättigter wäßriger Natriumchloridlösung, trocknet über Natriumsulfat und engt im Vakuum ein. Säulenchromatographie des erhaltenen Rohprodukts an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan ergibt 7,704 g (29,60 mmol; 67%) 1b.
^{1}H-NMR ($CDCl_3$): δ = 1,12–1,20 (3H), 1,27 (3H), 1,48–1,90 (6H), 2,58 (2H), 3,30–4,00 (7H), 4,15 (2H), 4,60+4,70 (1H) ppm.

Beispiel 1c

(5R)-5-Methyl-4-Oxa-6-(tetrahydro-2H-pyran-2-yl(oxy))hexan-1-ol

[0085] Eine Lösung von 7,704 g (29,60 mmol) 1b in 70 ml Tetrahydrofuran wird bei 0°C zu einer Suspension von 1,7 g (44,80 mmol) Lithiumaluminiumhydrid in 100 ml Tetrahydrofuran getropft. Man läßt eine Stunde bei 0°C nachrühren und addiert dann 10 ml gesättigte wäßrige Ammoniumchloridlösung. Anschließend wird über Celite filtriert und im Vakuum eingeengt. Säulenchromatographie des erhaltenen Rohprodukts an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan ergibt 6,204 g (28,41 mmol; 96%) 1c.
^{1}H-NMR ($CDCl_3$): δ = 1,10–1,22 (3H), 1,45–1,90 (8H), 2,95 (1H), 3,30–4,05 (8H), 4,58–4,70 (1H) ppm.

Beispiel 1d

(5R)-5-Methyl-4-Oxa-6-(tetrahydro-2H-pyran-2-yl(oxy))hexan-1-al

[0086] Zu einer Lösung von 3,67 ml (42,62 mmol) Oxalylchlorid in 100 ml wasserfreiem Dichlormethan wird bei –70°C eine Lösung von 5,99 ml (85,25 mmol) Dimethylsulfoxid, in 10 ml Dichlormethan addiert. Man rührt 3 Minuten

bei –70°C nach und addiert dann eine Lösung von 6,204 g (28,41 mmol) 1c in 100 ml Dichlormethan. Man läßt weitere 30 Minuten bei –70°C nachrühren. Anschließend versetzt man mit 31,5 ml (227,36 mmol) Triethylamin, läßt 30 Minuten bei –50°C reagieren. Danach wird das Reaktionsgemisch auf gesättigte wäßrige Natriumhydrogencarbonatlösung gegossen. Es wird mit Dichlormethan extrahiert. Die organische Phase wird mit gesättigter wäßriger Natriumchloridlösung gewaschen und über Natriumsulfat getrocknet. Das erhaltene Rohprodukt (6,15 g, 100%) wird ohne Aufreinigung in die Folgestufe eingesetzt.

Beispiel 1e

(6R)-6-Methyl-5-oxa-7-(tetrahydro-2H-pyran-2-yl(oxy))heptan-2-ol

[0087] 19 ml (57 mmol) einer 3 molaren Lösung von Methylmagnesiumchlorid in Tetrahydrofuran werden mit 80 ml Tetrahydrofuran verdünnt. Anschließend kühlt man auf 0°C und addiert eine lösung von 6,15 g (28,41 mmol) der unter 1d beschriebenen Verbindung in 70 ml Tetrahydrofuran. Man rührt 30 Minuten bei 0°C nach und gießt dann das Reaktionsgemisch auf gesättigte wäßrige Ammoniumchloridlösung. Anschließend wird mit Ethylacetat extrahiert. Die organische Phase wird mit gesättigter wäßriger Natriumchloridlösung gewaschen und über Magnesiumsulfat getrocknet. Säulenchromatographie des erhaltenen Rohprodukts an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan ergibt 6,008 g (25,86 mmol; 91%) 1e.
^{1}H-NMR ($CDCl_3$): δ = 1,12–1,22 (6H), 1,50–1,90 (8H), 3,32–4,07 (8H), 4,58–4,69 (1H) ppm.

Beispiel 1f

(6R)-6-Methyl-5-oxa-7-(tetrahydro-2H-pyran-2-yl(oxy))heptan-2-on

[0088] Eine Lösung von 6,008 g (25,86 mmol) der unter 1e beschriebenen Verbindung, 5,38 g (46,02 mmol) N-Methylmorpholino-N-oxid, 407 mg (1,16 mmol) Tetrapropylammoniumperruthenat in 200 ml Dichlormethan wird mit Molekularsieb (4A, ca. 600 Kugeln) versetzt. Man läßt 20 Stunden bei 25°C nachrühren. Anschließend wird im Vakuum eingeengt. Das erhaltene Rohprodukt wird durch Säulenchromatographie an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan gereinigt. Man erhält 5,892 g (25,60 mmol; 99%) 1f.
^{1}H-NMR ($CDCl_3$): δ = 1,11–1,18 (3H), 1,45–1,88 (6H), 2,18 (3H), 2,67 (2H), 3,30–3,98 (7H), 4,59 + 4,70 (1H) ppm.

Beispiel 1g

(2R,6Z,9S,10Z)-2,6-Dimethyl-9-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-10-fluor-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-dien-1-ol-tetrahydropyran-2-yl-ether (A)

(2R,6E,9S,10Z)-2,6-Dimethyl-9-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-10-fluor-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-dien-1-ol-tetrahydropyran-2-yl-ether (B)

[0089] Zu einer Suspension von 4,498 g (7,81 mmol) (3S,4Z)-5-(2-Methylthiazol-4-yl)-3-(tert.-butyl-dimethylsiloxy)-4-fluor-4-penten-triphenylphosphoniumiodid in 35 ml Tetrahydrofuran wird bei 0°C eine Lösung von Butyllithium in Hexan getropft (3,73 ml; 9,33 mmol; 2,5 M). Man läßt 30 Minuten nachrühren und addiert dann eine Lösung von 1,5 g (6,51 mmol) der unter 1f beschriebenen Verbindung in 35 ml Tetrahydrofuran. Anschließend wird 3 Stunden bei 0°C nachgerührt. Danach wird das Reaktionsgemisch auf gesättigte wäßrige Ammoniumchloridlösung gegossen. Man extrahiert mit Ethylacetat, wäscht die organische Phase mit gesättigter wäßriger Natriumchloridlösung und trocknet über Natriumsulfat. Das erhaltene Rohprodukt wird durch Säulenchromatographie an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan gereinigt. Man erhält 1,043 g (1,98 mmol; 30%) der Titelverbindung A und 870 mg (1,65 mmol; 25%) der Titelverbindung B.
Verbindung A: ^{1}H-NMR ($CDCl_3$): δ = 0,07 (6H), 0,90 (9H), 1,12–1,20 (3H), 1,45–1,67 (5H), 1,71 (3H), 1,81 (1H), 2,24–2,51 (4H), 2,70 (3H), 3,30–3,77 (5H), 3,81–4,00 (1H), 4,17–4,27 (1H), 4,61 (1H), 5,23 (1H), 5,99–6,12 (1H), 7,34 (1H) ppm.
Verbindung B: ^{1}H-NMR ($CDCl_3$): δ = 0,09 (6H), 0,90 (9H), 1,11–1,20 (3H), 1,48–1,61 (4H), 1,62 (3H), 1,68–1,90 (2H), 1,22–1,32 (2H), 1,39–1,47 (2H), 2,70 (3H), 3,28–3,65 (5H), 3,80–3,99 (1H), 1,16–4,27 (1H), 4,61 (1H), 5,21 (1H), 5,98–6,12 (1H), 7,33 (1H) ppm.

Beispiel 1h

(2R,6Z,9S,10Z)-2,6-Dimethyl-9-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-10-fluor-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-dien-1-ol

[0090] Eine Lösung von 1,043 g (1,98 mmol) der unter 1g beschriebenen Verbindung A und 990 mg (3,94 mmol) p-Toluolsulfonsäure-Pyridiniumsalz in 50 ml Ethanol wird 2 Stunden bei 50°C gerührt. Anschließend verdünnt man mit Dichlormethan. Die organische Phase wird mit gesättigter wäßriger Natriumhydrogencarbonatlösung und mit gesättigter wäßriger Natriumchloridlösung gewaschen. Man trocknet über Natriumsulfat. Das erhaltene Rohprodukt wird durch Säulenchromatographie an Kieselgel mit einem Gemisch aus EthylacetatlHexan gereinigt. Man erhält 702 mg (1,58 mmol; 80%) %) 1 h.
^{1}H-NMR ($CDCl_3$): δ = 0,09 (6H), 0,91 (9H), 1,10 (3H), 1,72 (3H), 2,28–2,37 (2H), 2,40–2,51 (2H), 2,70 (3H), 3,35–3,65 (5H), 4,17–4,28 (1H), 5,28 (1H), 6,00–6,13 (1H), 7,34 (1H) ppm.

Beispiel 1i

(2R,6Z,9S,10Z)-2,6-Dimethyl-9-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-10-fluor-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-dien-1-al

[0091] In Analogie zu Beispiel 1d werden aus 702 mg (1,58 mmol) 1 h 698 mg (1,58 mmol; 100%) rohes 1i erhalten, welches ohne Aufreinigung in die Folgestufe eingesetzt wird.
^{1}H-NMR ($CDCl_3$): δ = 0,07 (6H), 0,88 (9H), 1,25 83H), 1,70 (3H), 2,23–2,48 (4H), 2,69 (3H), 3,44–3,59 (2H), 3,72 (1H), 4,14–4,26 (1H), 5,25 (1H), 5,98–6,11 (1H), 7,31 (1H), 9,61 (1H) ppm.

Beispiel 1k

(3S,6R,7S,8R,12Z,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4, 4,6,8,12-pentamethyl-1,3,15-tris[(dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-dien-7-ol (A)

(3S,6S,7R,8R,12Z,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-1,3,7,15-tris[[dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-dien-7-ol (B)

[0092] Aus 473 mg (3,37 mmol) Diisopropylamin und 1,37 ml (3,41 mmol) einer 2,5 molaren Lösung von Butyllithium in Hexan wird in 20 ml absolutem Tetrahydrofuran Lithiumdiisopropylamid hergestellt. Man addiert dann bei –70°C eine Lösung von 1,273 g (3,16 mmol) (3S)-1,3-Bis[(dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4-dimethylheptan-5-on in 15 ml Tetrahydrofuran und läßt eine Stunde bei –40 bis –30°C nachrühren. Anschließend kühlt man erneut auf –70°C und tropft man eine Lösung von 698 mg (1,58 mmol) 1i in 15 ml Tetrahydrofuran langsam hinzu. Man läßt eine Stunde bei –70°C nachrühren und gießt dann das Reaktionsgemisch auf gesättigte wäßrige Ammoniumchloridlösung. Man extrahiert mit Ethylacetat, wäscht die organische Phase mit gesättigter wäßriger Natriumchloridlösung und trocknet über Natriumsulfat. Das erhaltene Rohprodukt wird durch Säulenchromatographie an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan gereinigt. Man erhält 494 mg (0,59 mmol; 37%) der Titelverbindung A und 464 mg (0,55 mmol; 35%) der Titelverbindung B.
Verbindung A: ^{1}H-NMR ($CDCl_3$): δ = 0,00–0,18 (18H), 0,84.0,99 (27H), 1,05 (3H), 1,08–1,18 (6H), 1,21 (3H), 1,71 (3H), 2,20–2,47 (4H), 2,69 (3H), 3,18–3,36 (3H), 3,50–3,70 (4H), 3,90 (1H), 4,15–4,28 (1H), 5,24 (1H), 5,98–6,12 (1H), 7,32 (1H) ppm.
Verbindung B: ^{1}H-NMR ($CDCl_3$): δ = 0,02–0,15 (18H), 0,85–0,94 (27H), 1,05 (3H), 1,08 (3H), 1,15 (3H), 1,20 (3H), 1,75 (3H), 2,30 (2H), 2,37–2,52 (2H), 2,70 (3H), 3,20–3,74 (7H), 4,09 (1H), 4,17–4,26 (1H), 5,25 (1H), 6,00–6,14 (1H), 7,34 (1H) ppm.

Beispiel 1l

(3S,6R,7S,8R,12Z,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-1,3,7,15-tetrakis([dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-dien

[0093] Zu einer Lösung von 494 mg (0,59 mmol) der unter 1k beschriebenen Verbindung A in 30 ml Dichlormethan werden bei –10°C 135p1 (1,17 mmol) 2,6-Lutidin und 161 µl (0,70 mmol) ml Trifluormethansulfonsäure-tert.butyldimethylsilylester addiert. Man läßt 2 Stunden bei 0°C nachrühren. Danach wird das Reaktionsgemisch auf gesättigte wäßrige Natriumhydrogencarbonatlösung gegossen. Man extrahiert mit Dichlormethan, wäscht die organische Phase mit gesättigter wäßriger Natriumchloridlösung, trocknet über Natriumsulfat und engt im Vakuum ein. Das erhaltene Rohprodukt wird durch Säulenchromatographie an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan gereinigt. Man erhält 527 g (0,55 mmol; 93%) 1l.
^{1}H-NMR ($CDCl_3$): δ = 0,00–0,15 (24H), 0,82–0,97 (36H), 1,03 (3H), 1,06 (3H), 1,11 (3H), 1,28 (3H), 1,69 (3H), 2,22–2,46 (4H), 2,70 (3H), 3,18–3,40 (4H), 3,52–3,72 (2H), 3,80 (1H), 3,99 (1H), 4,13–4,27 (1H), 5,22 (1H), 5,99–6,12 (1H), 7,33 (1H) ppm.

Beispiel 1m

(3S,6R,7S,8R,12Z,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-3,7,15-tris[[dimethyl(1,1-dimethylethyl)silyl]oxy] heptadeca-12,16-dien-1-ol

[0094] Eine Lösung von 527 mg (0,55 mmol) 11 und 128 mg (0,55 mmol) Campher-10-sulfonsäure in 20 ml eines 1 : 1 Gemisches aus Dichlormethan und Methanol wird 2 Stunden bei 25°C gerührt. Anschließend addiert man einen Überschuß Triethylamin und engt im Vakuum ein. Das erhaltene Rohprodukt wird durch Säulenchromatographie an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan gereinigt. Man erhält 404 mg (0,48 mmol; 87%) 1 m.
^{1}H-NMR ($CDCl_3$): δ = 0,03–0,14 (18H), 0,85–0,95 (27H), 1,06 (3H), 1,08–1,15 (6H), 1,24 (3H), 1,71 (3H), 2,11–2,35 (3H), 2,42 (2H), 2,69 (3H), 3,15–3,40 (4H), 3,59–3,69 (2H), 3,99–4,06 (2H), 4,14–4,25 (1H), 5,21 (1H), 5,99–6,12 (1H), 7,34 (1H) ppm.

Beispiel 1n

(3S,6R,7S,8R,12Z,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-3,7,15-tris[[dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-dien-1-al

[0095] Analog zu Beispiel 1d werden aus 404 mg (0,48 mmol) der unter Beispiel 1 m beschriebenen Substanz 403 mg (0,48 mmol, 100%) 1 n erhalten. Die Substanz wird ohne Aufreinigung in die Folgestufe eingesetzt.
^{1}H-NMR ($CDCl_3$): δ = 0,02–0,13 (18H), 0,83–0,92 (27H), 1,02 (3H), 1,09 (3H), 1,11 (3H), 1,39 (3H), 1,71 (3H), 2,10–2,31 (2H), 2,34–2,45 (3H), 2,58–2,63 (1H), 2,71 (3H), 3,14–3,40 (4H), 4,01 (1H), 4,14–4,26 (1H), 4,49 (1H), 5,22 (1H), 5,99–6,12 (1H), 7,34 (1H) ppm.

Beispiel 1o

(3S,6R,7S,8R,12Z,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-3,7,15-tris[[dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-diensäure

[0096] Eine Lösung von 403 mg (0,48 mmol) der unter 1 n beschriebenen Substanz in 15 ml tert.-Butanol wird mit 13,7 ml 2-Methyl-2-buten (27,4 mmol) versetzt. Man kühlt dann auf 2°C und addiert 3,7 ml Wasser, 198 mg (1,44 mmol) Natriumdihydrogenphosohat-Monohydrat, 336 mg Natriumchlorit (2,97 mmol) und läßt eine 1 Stunde bei 2°C nachrühren. Anschließend gießt man in gesättigte Natriumthiosulfatlösung, verdünnt mit Wasser und extrahiert mehrfach mit Ethylacetat. Die vereinigten organischen Extrakte trocknet man über Natriumsulfat und reinigt den nach Filtration und Lösungsmittelabzug erhaltenen Rückstand durch Chromatographie an feinem Kieselgel mit einem Gradientensystem aus n-Hexan und Ethylacetat. Man erhält 345 mg (0,40 mmol, 84%) 1o.
^{1}H-NMR ($CDCl_3$): δ = 0,04–0,15 (18H), 0,86–0,94 (27H), 1,05 (3H), 1,14 (3H), 1,18 (3H), 1,28 (3H), 1,71 (3H), 2,05 (3H), 2,26–2,48 (4H), 2,63–2,71 (1H), 2,72 (3H), 3,10–3,42 (4H), 4,08 (1H), 4,13–4,26 (1H), 4,37 (1H), 5,23 (1H), 6,20–6,33 (1H), 7,33 (1H) ppm.

Beispiel 1p

(3S,6R,7S,8R,12Z,15S,16Z)-3,7-Bis[[dimethyl(1,1-dimethylethyl)silyl)oxy]-16-fluor-15-hydroxy-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-12,16-diensäure

[0097] Eine Lösung von 345 mg (0,40 mmol) 10 in 15 ml Tetrahydrofuran wird mit 6 ml einer 1 molaren lösung von Tetrabutylammoniumfluorid in Tetrahydrofuran versetzt. Man läßt eine Stunde bei 25°C nachrühren und gießt dann das reaktionsgemisch auf eiskalte gesättigte wäßrige Ammoniumchloridlösung. Man extrahiert mit Ethylacetat und wäscht die organische Phase mit 1 normaler Salzsäure und gesättigter wäßriger Natriumhydrogencarbonatlösung. Danach wird über Natriumsulfat getrocknet. Das erhaltene Rohprodukt (299 mg; 0,40 mmol; 100%) wird ohne Aufreinigung in die Folgestufe eingesetzt.
^{1}H-NMR ($CDCl_3$): δ = 0,03–0,13 (12H), 0,86–0,92 (18H), 1,06 (3H), 1,11 (3H), 1,16 (3H), 1,28 (3H), 1,73 (3H), 2,27–2,59 (6H), 2,71 (3H), 3,08–3,17 (1H), 3,30–3,49 (3H), 4,08 (1H), 4,21–4,30 (1H), 4,37 (1H), 5,28 (1H), 6,28–6,42 (1H), 7,33 (1H) ppm.

Beispiel 1q

4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethylcyclohexadec-13-en-2,6-dion

[0098] Zu einer Lösung von 299 mg (0,40 mmol) der unter 1p beschriebenen Verbindung 4 ml Tetrahydrofuran werden 334 µl (2,40 mmol) Triethylamin und 315 µl (2,01 mmol) 2,4,6-Trichlorbenzoylchlorid addiert. Man läßt 15 Minuten bei 25°C nachrühren und verdünnt dann mit 35 ml Toluol. Diese Lösung wird über 3 Stunden zu einer Lösung von 510 mg (4,18 mmol) N,N-Dimethylaminopyridin in 100 ml Toluol hinzugetropft. Nach vollständiger Zugabe wird eine weitere Stunde bei 25°C nachgerührt. Anschließend wird das Reaktionsgemisch im Vakuum eingeengt. Nach Säulenchromatographie werden 169 mg (0,23 mmol, 58%) der Titelverbindung erhalten.
^{1}H-NMR ($CDCl_3$): δ = 0,02–0,14 (12H), 0,85–0,93 (18H), 1,07 (3H), 1,12 (3H), 1,19–1,24 (6H), 1,67 (3H), 2,00–2,10 (1H), 2,41–2,65 (3H), 2,7C) (3H), 2,76–2,88 (1H), 3,14–3,23 (1H), 3,39–3,53 (3H), 4,02 (1H), 4,34 (1H), 5,23 (1H), 5,46–5,56 (1H), 6,09–6,12 (1H), 7,38 (1H) ppm.

Beispiel 1

4S,7R,8S,9R,13(Z),16S(Z))-4,8-Bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethylcyclohexadec-13-en-2,6-dion

[0099] Zu einer Lösung von 169 mg (0,23 mmol) der unter 1d beschriebenen Verbindung in 10 ml Tetrahydrofuran werden bei 0°C 530 µl HF-Pyridin-Komplex addiert. Man rührt eine Stunde bei 25°C und addiert dann erneut 530 µl HF-Pyridin-Komplex. Anschließend läßt man 10 Stunden bei 25°C nachrühren. Danach wird das Reaktionsgemisch auf gesättigte wäßrige Natriumhydrogencarbonatlösung gegossen. Man extrahiert mit Dichlormethan, wäscht die organische Phase mit gesättigter wäßriger natriumchloridlösung und trocknet über Natriumsulfat. Säulenchromatographie an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan ergibt 80 mg (0,16 mmol; 69%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,11 (3H), 1,19 (3H), 1,23 (3H), 1,31 (3H), 1,71 (3H), 2,06–2,17 (1H), 2,38–2,68 (4H), 2,70 (3H), 2,73–2,87 (1H), 3,00 (1H), 3,19–3,31 (2H), 3,48 (1H), 3,74–3,84 (2H), 4,12–4,22 (1H), 5,38–5,49 (1H), 6,10–6,13 (1H), 7,38 (1H) ppm.

Beispiel 2

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion (A)

(1R,3S(Z),7S,10R,11S,12R,16S)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion (B)

[0100] Eine Lösung von 20 mg (0,04 mmol) der unter Beispiel 1 beschriebenen Verbindung in 2 ml Acetonitril wird mit 237 µl einer 1 M Lösung von Natriumethylendiamin-tetracetat versetzt. Man kühlt auf 0°C und addiert dann 440 µl (4,91 mmol) 1,1,1-Trifluoraceton sowie ein Gemisch aus 121 mg (0,20 mmol) Oxon und 28 mg (0,33 mmol) Natriumhydrogencarbonat. Man läßt 2 Stunden bei 2°C nachrühren und gießt dann auf Natriumthiosulfatlösung. Man extrahiert mit Ethylacetat, wäscht die organische Phase mit gesättigter wäßriger Natriumchloridlösung und trocknet über Natriumsulfat. Nach Säulenchromatographie an Kieselgel mit einem Gemisch aus Ethylacetat/Hexan werden 10 mg (0,019 mmol; 49%) der Titelverbindung A sowie 5 mg (0,01 mmol; 24%) der Titelverbindung B erhalten.
Verbindung A: ^{1}H-NMR ($CDCl_3$): δ = 1,02 (3H), 1,11 (3H), 1,24 (3H), 1,30 (3H), 1,40 (3H), 1,63–1,74 (1H), 1,78–1,86 (1H), 1,99–2,08 (1H), 2,23–2,31 (1H), 2,50–2,56 (1H), 2,61-2,68 (1H), 2,72 (3H), 2,93 (1H), 3,43–3,59 (4H), 3,60–3,66 (1H), 3,72–3,78 (1H), 4,20 (1H), 4,56 (1H), 5,70–5,77 (1H), 6,21–6,32 (1H), 7,38 (1H) ppm.
Verbindung B: ^{1}H-NMR ($CDCl_3$): δ = 1,07 (3H), 1,14 (3H), 1,21 (3H), 1,27 (3H), 1,31 (3H), 1,72–1,81 (1H), 1,83–1,91 (1H), 2,08–2,17 (1H), 2,23–2,31 (1H), 2,57–2,65 (2H), 2,71 (3H), 2,89 (1H), 3,00 (1H), 3,46–3,58 (1H), 3,65 (1H), 3,83–3,90 (1H), 4,18 (1H), 5,78–5,86 (1H), 6,18–6,28 (1H), 7,40 (1H) ppm.

Beispiel 3

4S,7R,8S,9R,13(E),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethylcyclohexadec-13-en-2,6-dion

Beispiel 3a

(2R,6E,9S,10Z)-2,6-Dimethyl-9-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-10-fluor-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-dien-1-ol

[0101] Analog zu Beispiel 1h werden aus 870 mg (1,65 mmol) der unter Beispiel 1g beschriebenen Verbindung B 600 mg (1,35 mmol; 82%) der Titelverbindung erhalten.
^{1}H-NMR ($CDCl_3$): δ = 0,08–0,12 (6H), 0,91 (9H), 1,09 (3H), 1,63 (3H), 2,27 (2H), 2,44 (2H), 2,70 (3H), 3,37–3,68 (5H), 4,17–4,29 (1H), 5,23 (1H), 5,98–6,12 (1H), 7,33 (1H) ppm.

Beispiel 3b

(2R,6E,9S,10Z)-2,6-Dimethyl-9-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-10-fluor-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-dien-1-al

[0102] Analog zu Beispiel 1d werden aus 600 mg (1,35 mmol) der unter 3a beschriebenen Verbindung 596 mg (1,35 mmol, 100%roh) der Titelverbindung erhalten.

Beispiel 3c

(3S,6R,7S,8R,12E,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-1,3,15-tris[[dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-dien-7-ol (A)

(3S,6S,7R,8R,12E,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-1,3,7,15-tris[[dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-dien-7-ol (B)

[0103] Analog zu Beispiel 1k werden aus 596 mg (1,35 mmol) der unter 3b beschriebenen Verbindung 464 mg (0,55 mmol; 41%) der Titelverbindung A und 388 mg (0,46 mmol; 34%) der Titelverbindung B erhalten.
Verbindung A: ^{1}H-NMR ($CDCl_3$): δ = 0,00–0,16 (18H), 0,86–0,99 (27H), 1,05 (3H), 1,11 (3H), 1,15 (3H), 1,22 (3H), 1,62 (3H), 2,25 (2H), 2,41 (2H), 2,53 (1H), 2,69 (3H), 3,18–3,37 (3H), 3,48–3,73 (4H), 3,90 (1H), 4,15–4,28 (1H), 5,21 (1H), 5,98–6,10 (1H), 7,33 (1H) ppm.
Verbindung B: ^{1}H-NMR ($CDCl_3$): δ = 0,00–0,18 (18H), 0,84–0,97 (27H), 1,03 (3H), 1,08 (3H), 1,17 (3H), 1,19 (3H), 2,24 (2H), 2,43 (2H), 2,70 (3H), 3,18–3,28 (2H), 3,42–3,52 (2H), 3,57–3,73 (3H), 4,07 (1H), 4,16–4,28 (1H), 5,22 (1H), 5,99–6,12 (1H), 7,32 (1H) ppm.

Beispiel 3d

(3S,6R,7S,8R,12E,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-1,3,7,15-tetrakis[[dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-dien

[0104] Analog zu Beispiel 1l werden aus 464 mg (0,55 mmol) der unter 3c beschriebenen Verbindung A 485 mg (0,51 mmol, 92%) der Titelverbindung erhalten.
^{1}H-NMR ($CDCl_3$): δ = –0,02–0,13 (24H), 0,82–0,96 (36H), 0,98–1,04 (6H), 1,10 (3H), 1,28 (3H), 1,62 (3H), 2,17 (2H), 2,40 (2H), 2,69 (3H), 3,20 (1H), 3,28–3,39 (3H), 3,52–3,72 (2H), 3,80 (1H), 3,98 (1H), 4,01–4,26 (1H), 5,18 (1H), 5,98–6,11 (1H), 7,31 (1H) ppm.

Beispiel 3e

(3S,6R,7S,8R,12E,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-3,7,15-tris[[dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-dien-1-ol

[0105] Analog zu Beispiel 1m werden aus 485 mg (0,51 mmol) der unter 3d beschriebenen Verbindung 370 mg (0,44 mmol, 86%) der Titelverbindung erhalten.
^{1}H-NMR ($CDCl_3$): δ = 0,02–0,17 (18H), 0,84–0,97 (2TH), 1,04 (3H), 1,07–1,14 (6H), 1,22 (3H), 1,61 (3H), 2,17 (2H), 2,41 (2H), 2,70 (3H), 3,20 (1H), 3,30–3,42 (3H), 3,59–3,70 (2H), 4,02 (2H), 4,13–4,29 (1H), 5,18 (1H), 5,98–6,10 (1H), 7,32 (1H) ppm.

Beispiel 3f

(3S,6R,7S,8R,12E, 15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-3,7,15-tris[[dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-dien-1-al

[0106] Analog zu Beispiel 1d werden aus 370 mg (0,44 rnmol) der unter 3e beschriebenen Verbindung 370 mg (0,44 mmol, 100% roh) der Titelverbindung erhalten.
^{1}H-NMR ($CDCl_3$): δ = 0,01–0,15 (18H), 0,82–0,95 (27H), 1,01 (3H), 1,05–1,12 (6H), 1,27 (3H), 1,61 (3H), 2,15 (2H), 2,42 (2H), 2,56–2,67 (1H), 2,70 (3H), 3,17 (1H), 3,28–3,41 (3H), 4,00 (1H), 4,13–4,28 (1H), 4,40 (1H), 5,18 (1H), 5,98–6,11 (1H), 7,32 (1H) ppm.

Beispiel 3g

(3S,6R,7S,8R,12E,15S,16Z)-16-Fluor-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4, 4,6,8,12-pentamethyl-3,7,15-tris[[dimethyl(1,1-dimethylethyl)silyl]oxy]heptadeca-12,16-diensäure

[0107] Analog zu Beispiel 1o werden aus 370 mg (0,44 mmol) der unter 3f beschriebenen Verbindung 302 mg (0,35 mmol, 80%) der Titelverbindung erhalten.
^{1}H-NMR ($CDCl_3$): δ = 0,00–0,16 (18H), 0,82–0,98 (27H), 1,05 (3H), 1,10 (3H), 1,15 (3H), 1,21 (3H), 1,61 (3H), 2,15 (2H), 2,25–2,53 (3H), 2,63–2,76 (1H), 2,72 (3H), 3,17 (1H), 3,28–3,44 (3H), 4,07 (1H), 4,16–4,28 (1H), 4,34 (1H), 5,21 (1H), 6,07–6,20 (1H), 7,35 (1H) ppm.

Beispiel 3h

(3S,6R,7S,8R,12E,15S,16Z)-3,7-Bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-16-fluor-15-hydroxy-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-12,16-diensäure

[0108] Analog zu Beispiel 1p werden aus 302 mg (0,35 mmol) der unter 3g beschriebenen Verbindung 260 mg (0,35 mmol, 100% roh) der Titelverbindung erhalten.
^{1}H-NMR ($CDCl_3$): δ = 0,02–0,13 (12H), 0,83–0,98 (18H), 1,04 (3H), 1,08–1,17 (6H), 1,24 (3H), 1,63 (3H), 2,16 (1H), 2,22–2,35 (1H), 2,42–2,69 (3H), 2,69 (3H), 3,11 (1H), 3,30–3,47 (3H), 3,99–4,14 (1H), 3,27–3,47 (2H), 5,22 (1H), 6,18–6,32 (1H), 7,33 (1H) ppm.

Beispiel 3i

4S,7R,8S,9R,13(E),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethylcyclohexadec-13-en-2,6-dion

[0109] Analog zu Beispiel 1q werden aus 260 mg (0,35 mmol) der unter 3h beschriebenen Verbindung 175 mg (0,24 mmol, 69%) der Titelverbindung erhalten.
^{1}H-NMR ($CDCl_3$): δ = 0,03–0,16 (12H), 0,85–0,94 (18H), 1,06 (3H), 1,09–1,16 (6H), 1,18 (3H), 1,63 (3H), 2,02–2,29 (2H), 2,38–2,46 (1H), 2,53–2,63 (2H), 2,67–2,82 (1H), 2,68 (3H), 3,08 (1H), 3,33–3,48 (2H), 3,55–3,62 (1H), 4,00 (1H), 4,43 (1H), 5,29 (1H), 5,46–5,57 (1H), 6,12–6,24 81 H), 7,38 (1H) ppm.

Beispiel 3

4S,7R,8S,9R,13(E),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethylcyclohexadec-13-en-2,6-dion

[0110] Analog zu Beispiel 1 werden aus 175 mg (0,24 mmol) der unter 3i beschriebenen Verbindung 85 mg (0,17 mmol, 71%) derTitelverbindung erhalten.
^{1}H-NMR ($CDCl_3$): δ = 1,06 (3H), 1,17 (3H), 1,24 (3H), 1,30 (3H), 1,69 (3H), 2,23 (2H), 2,48–2,61 (2H), 2,61–2,77 (2H), 2,70 (3H), 3,28–3,45 (3H), 3,52 (1H), 3,67–3,79 (2H), 4,21 (1H), 5,23 (1H), 5,53–5,63 (1H), 6,12–6,26 (1H), T,39 (1H) ppm.

Beispiel 4

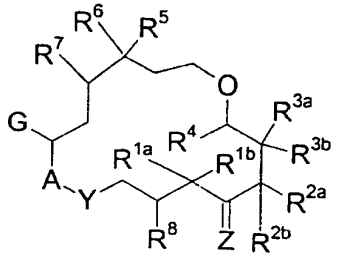
(1S,3S(Z),7S,10R,11S,12R,16S)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion (A)

(1R,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion (B)

[0111] Analog zu Beispiel 2 werden aus 50 mg (0,10 mmol) der unter Beispiel 3 beschriebenen Verbindung 19 mg (0,037 mmol, 37%) der Titelverbindung A und 14 mg (0,027 mmol, 27%) der Titelverbindung B erhalten.
Verbindung A: ^{1}H-NMR ($CDCl_3$): δ = 1,11 (3H), 1,17–1,25 (6H), 1,28 (3H), 1,36 (3H), 1,52–1,61 (1H), 2,08–2,22 (3H), 2,45 (1H), 2,69 (3H), 2,76–2,85 (1H), 2,98–3,08 (2H), 3,17–3,37 (2H), 3,46–3,60 (2H), 3,69 (1H), 4,31 (1H), 5,61–5,73 (1H), 6,16–6,28 (1H), 7,39 (1H) ppm.
Verbindung B: ^{1}H-NMR ($CDCl_3$): δ = 1,02 (3H), 1,17 (3H), 1,22 (3H), 1,29 (3H), 1,36 (3H), 1,55–1,79 (3H), 1,95–2,35 (3H), 2,47–2,63 (2H), 2,69 (3H), 2,94 (1H), 3,09 (1H), 3,16–3,27 (1H), 3,38–3,48 (1H), 3,54–3,69 (3H), 4,16 (1H), 4,32 (1H), 5,62–5,73 (1H), 6,19–6,32 (1H), 7,39 (1H) ppm.

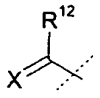
Patentansprüche

1. Epothilon-Derivate der allgemeinen Formel I,



I,

worin
R^{1a}, R^{1b} gleich oder verschieden sind und Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, oder gemeinsam eine -$(CH_2)_m$-Gruppe mit m = 1, 2, 3, 4 oder 5, oder eine -(CH_2)-O-(CH_2)-Gruppe,
R^{2a}, R^{2b} gleich oder verschieden sind und Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, -$(CH_2)_r$-C≡C-$(CH_2)_p$-R^9, -$(CH_2)_r$-C=C-$(CH_2)_p$-R^9,
r gleich 0 bis 4,
p gleich 0 bis 3,
R^9 Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, C_1-C_{10}-Acyl, oder, falls p>0 ist, auch eine Gruppe OR^{10},
R^{10} Wasserstoff, eine Schutzgruppe PG^{10},
R^{3a} Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl,
R^{3b} OH, OPG^3
R^4 Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl
R^5 Wasserstoff, C_1-C_{10}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, Halogen, Cyano, $(CH_2)_s$-T, wobei s für 1, 2, 3 oder 4,
T für OR^{11} oder Hal,
R^{11} für Wasserstoff oder PG^{11} stehen,
R^6, R^7 je ein Wasserstoffatom, gemeinsam eine zusätzliche Bindung oder ein Sauerstoffatom,
G eine Gruppe



ein bi- oder tricyclischer Arylrest,
R^{12} Wasserstoff, Halogen, CN, C_1-C_{20}-Alkyl, Aryl, C_7-C_{20}-Aralkyl, die alle substituiert sein können,
X ein Sauerstoffatom, zwei Alkoxygruppen OR^{13}, eine C_2-C_{10}-Alkylen-α,ω-dioxygruppe, die geradkettig oder verzweigt sein kann, H/OR^{14} oder eine Gruppierung $CR^{15}R^{16}$,
wobei
R^{13} für einen C_1-C_{20}-Alkylrest,
R^{14} für Wasserstoff oder eine Schutzgruppe PG^{14},
R^{15}, R^{16} gleich oder verschieden sind und für Wasserstoff, einen C_1-C_{20}-Alkyl-, Aryl-, C_7-C_{20}-Aralkylrest stehen,
A-Y eine Gruppe O-C(=O), O-CH_2, CH_2C(-O), NR^{17}-C(=O), NR^{17}-SO_2,
R^{17} Wasserstoff, C_1-C_{10}-Alkyl,
Z ein Sauerstoffatom oder H/OR^{18},
wobei
R^{18} Wasserstoff oder eine Schutzgruppe PG^{18} ist,
R^8 OH oder OPG^8
Hal Halogen, vorzugsweise Fluor, Chlor oder Brom bedeutet
ausgenommen derjenigen Verbindungen, in denen R^{2a} Wasserstoff ist und R^{2b} Wasserstoff, Alkyl oder Aryl und gleichzeitig
R^5 Wasserstoff, Alkyl oder Aryl und gleichzeitig A-Y eine Gruppierung O-C(=O), O-CH_2 oder NR^{17}-C(=O) und gleichzeitig G einen bi- oder tricyclischen Arylrest oder eine Gruppierung X=(CR^{12})- bedeuten, wobei alle anderen Reste die angegebenen Bedeutungen haben können.

2. Epothilon-Derivate der allgemeinen Formel I nach Anspruch 1, nämlich
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-pyridyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluor-2-(2-pyridyl)ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-fluor-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-pyridyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-7-ethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-

5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxydroxy-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-7-ethyl-16-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-fluor-2-(2-pyridyl)ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-7-ethyl-16-(1-fluor-2-(2-pyridyl)ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-fluor-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-fluor-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-pyridyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-7-ethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-eithyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-7-ethyl-16-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa16-(1-chlor-2-(2-pyridyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-7-ethyl-16-(1-chlor-2-(2-pyridyl)ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-chlor-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16(1-chlor-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-pyridyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-

5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-7-ethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-7-ethyl-16(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-pyridyl)ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-Chlor-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-7-ethyl-16-(1-chlor-2-(2-pyridyl)ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-10-ethyl-3-(1-chlor-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexaciec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1.-chlor-2-(2-pyridyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-7,9,13-trimethyl-5,5-(1,3-trimethylera)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-deca-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-7-ethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-10-ethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-7,9,13-trimethyl-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-deca-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-7-ethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-10-ethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-7,9,13-trimethyl-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo(14.1.0]hepta-deca-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-7-ethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-10-ethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy1,10-dioxa-9,13-dimethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethe-

nyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-7,9,13-trimethyl-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-deca-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-7-ethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-10-ethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridy4)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,35(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-meth yloxazol-4-yl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-

5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1. 0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0)hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(but-2-in-1-yl)-5,5,9,13-tetramethyl-cydohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(but-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyloxazol-4-yl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexaclec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazo-

lyl)ethenyl)-7-(but-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-5-benzoxazolyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo(14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo(14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5, 5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(but-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-i n-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0] heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-in-1-yl)-1-

aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-5-benzothiazolyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S, 10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-in-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5- benzothiazolyl)-7-(but-2-en-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-en-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-d ioxabicyclo[14.1.0]heptadeca n-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-en-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-en-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-16-(2-methyl-5- benzothiazolyl)-7-(but-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-in-1-yl)-5,5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4,13,17-trioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-Dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-in-1-yl)-1-aza-10-oxa-5, 5-(1,3-trimethylen)cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-in-1-yl)-8,8-(1,3-trimethylen)-4-aza-13,17-dioxabicyclo[14.1.0]hepta-decan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-13-fluor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-

5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-13-fluor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Fluor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxalbicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Fluor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-13-chlor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-13-chlor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-ethyl-13-fluor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Fluor-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Fluor-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-7-allyl-13-chlor-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Chlor-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Chlor-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12-trimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,5S,9S, 13E,16S(E))-4,8-Dihydroxy-13-chlor-16-(1-methyl-2-(2-methyl-2-pyridyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(E),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(E),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-trimethylen-1,10-dioxa-7,9-dimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-5,5-trimethylen-1,10-dioxa-7,9-dimethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-trimethylen-10,12-dimethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-4-oxazolyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-oxazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-oxazolyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo[14.1.0]heptadecan-5,9-dion
(4S,7R,8S,9S,13E,16S(Z))-4,8-Dihydroxy-13-chlor-16-(1-fluor-2-(2-methyl-2-pyridyl)ethenyl)-1,10-dioxa-5,5,7,9-tetraamethyl-cyclohexadec-13-en-2,6-dion
(1S,3S(Z),7S,10R,11S,12S,16S)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo(14.1.0]heptadecan-5,9-dion
(1R,3S(Z),7S,10R,11S,12S,16R)-16-Chlor-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-2-pyridyl)ethenyl)-8,8,10,12-

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The following dates were taken from the documents filed by the applicant.

54 9-oxa-epothilone derivatives, a method for their preparation as well as their use in pharmaceutical preparations.

57 This invention describes new epothilone derivatives which are characterized by an oxygen atom in position 9 of the basic epothilone structure.
The new compounds interact with tubuline by stabilizing the micro-tubulines that have formed. They are capable of affecting the cell division in a phase-specific manner and can be used to treat malignant tumors such as ovarian carcinoma, gastric c., colon c., adenocarcinoma, breast c., pulmonary carcinoma, head c. and neck c., malignant melanoma, acute lymphocytic and myelocytic leukemia. Furthermore, they can be used for the anti-angiogenesis therapy as well as to treat chronic inflammatory diseases (psoriasis, arthritis). To prevent an uncontrollable cell proliferation on medical implants as well as to improve the compatibility of medical implants, they can be applied on or in polymeric materials.
The compounds in accordance with the invention can be used alone or - to achieve cumulative or synergistic effects - in combination with other principles and substance classes which are utilized in the tumor therapy.

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Description

[0001] Von Höfle et al. describe the cytotoxic effect of the natural substances epothilone A (R = hydrogen) and epothilone B (R = methyl)

/formula/
Epothilone A (R=H), Epothilone B ($R=CH_3$)

in, for example, Applied Chemistry (Angew.Chem.) 1996, 108, 1671-1673. Because of their in vitro selectivity versus breast and intestine cell lines and their - in comparison with Taxol - distinctly higher activity against P-glycoprotein-forming and multi-resistant tumor lines as well as their improved physical properties in comparison with Taxol, e.g., their water solubility is 30 times greater, this new structure class is of particular interest for the development of a drug to be used in the therapy for malignant tumors.

[0002] Natural substances are neither chemically nor metabolically stable to a sufficient degree to permit a development of drugs. The natural substance must be modified to cancel out these disadvantages. Such modifications are possible only in a totally synthetic manner and require synthesis strategies that permit a broad modification of the natural substance. The target of changes in the structure also includes a broadening of the therapeutic width. This can be achieved by improving the selective effect and/or strengthening the effect and/or reducing undesired toxic side effects as described in Proc. Natl. Acad. Sci. USA 1998,9S,9642-9647.

[0003] The total synthesis of epothilone A has been described by Schinzer et al. in Chem. Eur. J. 1996, 2, No. 11, 1477-1482 and in Applied Chemistry 1997, 109, No. 5, Pages 543-544.

[0004] Epothilone derivatives have been described already by Höfle et al. in WO 97/19086. These derivatives were prepared on the basis of natural epothilone A or B. Epothilone C and D (double linkage between the carbon atoms 12 and 13; epothilone C = desoxy epothilone A; epothilone D = desoxy epothilone B) are described as possible source products for them.

[0005] Another synthesis for epothilone and epothilone derivatives was described by Nicolaou et al. in Applied Chemistry 1997, 109, No. 1/2, Pages 170-172. The synthesis of epothilone A and B and of some analogous epothilones was described in Nature, Vol. 387, 1997, Pages 268-272 and the synthesis of epothilone A and its derivatives was described in J.Am.Chem.Soc, Vol. 119, No. 34, 1997, Pages 7960-7973 and the synthesis of epothilone A and B and of some analogous epothilones was described in J.Am.Chem.Soc., Vol. 119, No. 34, 1997, Pages 7974-7991, i.e., also by Nicolaou et al.

[0006] Nicolaou et al. have also described in Applied Chemistry 1997, 109, No. 19, Pages 2181-2187, the preparation of analogous epothilone A with the help of a combinatorial solid-phase synthesis. Some analogous epothilones B are also described there.

[0007] Epothilone derivatives and in part also epothilone C and D are also described in patent applications WO 99/07692, WO 99/02514, WO 99/01124, WO 99/67252, WO 98/25929, WO 97119086, WO 98/38192, WO 99/22461 and WO 99/58534.

[0008] The task of this invention consists of providing new epothilone derivatives that are sufficiently stable in a chemical as well as metabolic manner to permit a drug development and that are superior to the natural derivatives with respect to their therapeutic range, their selectivity regarding effects and/or undesired toxic side effects and/or their strength of the effectiveness.

[0009] This invention describes the new epothilone derivatives of the general formula I,

/formula/

where
R^{1a}, R^{1b} are identical or different and hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or jointly a $(CH_2)_m$ group with m = 1,2,3,4 or 5, or a -(CH_2)-O-(CH_2)-group,
R^{2a}, R^{2b} are identical or different and hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, -$(CH_2)_r$-C≡C-$(CH_2)_p$-R^9, -
$(CH_2)_r$-C≡C-$CH_2)_p$-R^9,
r equals 0 to 4,
p equals 0 to 3,
R_9 hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, C_1-C_{10} acyl, or when p>0, also a group OR^{10},
R^{10} is hydrogen, a protective group PG^{10},
R^{3a} is hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,
R^{3b} stands for OH, OPG^3
R^4 is hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,
R^5 is hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, halogen, cyano, $(CH_2)_s$-T, in which case s is 1, 2, 3 or 4,
T for OR^{11} or halogen,
R^{11} stands for hydrogen or PG^{11},
R^6, R^7 each represents a hydrogen atom, together an additional linkage or an oxygen atom,
G is a group

/formula/

a bi- or tricyclic aryl rest,
R^{12} stands for hydrogen, halogen, CN, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl, all of which can be substituted,
X stands for an oxygen atom, two alkoxy groups OR^{13}, a C_2-C_{10} alkylene-α,w-dioxy group which can be linear or branched, H/OR^{14} or a grouping $CR^{15}R^{16}$,
in which case
R^{13} is a C_1-C_{20} alkyl rest,
R^{14} is hydrogen or a protective group PG^{14},
R^{15}, R^{16} are identical or different and stand for hydrogen, a C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl rest,
A-Y a group O-C(=O), O-CH_2, CH_2C(=O), NR^{17}-C(=O), NR^{17}-SO_2,
R^{17} is hydrogen, C_1-C_{10} alkyl
Z is an oxygen atom or H/OR^{18},
in which case
R^{18} is hydrogen or a protection group PG^{18},
R^8 stands for OH or OPG^8,

Hal halogen, preferably fluorine, chlorine or bromine,
with the exception of those compounds, in which R^{2a} is hydrogen and R^{2b} stands for hydrogen, alkyl or aryl and simultaneously stands for
R^5 is hydrogen, alkyl or aryl and simultaneously
A-Y is a grouping O-C(=O), O-CH_2 or NR^{17}-C(=O) and simultaneously
G stands for a bi- or tricyclic aryl rest or a grouping X=(CR^{12}), in which case all other rests have the indicated meaning.

[0010] The compounds claimed in WO 99/02514 are excluded on the basis of the disclaimer.

[0011] The compounds listed below are preferred in accordance with the invention:
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,7,9,13-penta-methyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12,16-penta methyl-4,13,17-trioxa bicyclo [14.1.0] heptadecan-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12,16-tetra-methyl-4,13,17-trioxa bicyclo [14.1.0] heptadecan-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,l3-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,10,12,16-penta methyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-h-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-pyridyl) ethenyl)-5,5,7,9,13-penta methyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-pyridyl) ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluoro-2-(2-pyridyl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-pyridyl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-pyridyl) ethenyl)-10-(prop-2-

ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-oza-13,17-dioxa bicyclo[14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,10,12,16-pentamethyl-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-methyl oxazol4-yl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-pyridyl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-fluoro-2-(2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-pyridyl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,7,9,13-penta-methyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methyl-4-thiazolyl)

ethenyl)-7-(prop-2-ene-1yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methylexazol-4-yl) ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-6-(1-chloro-2-(2-pyridyl) ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-pyridyl) ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-chloro-2-(2-pyridyl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-pyridyl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo[14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-chloro-2-(2-methyl oxazoltyl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-methyl oxazol-4-yl)

ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-pyridyl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-chloro-2-(2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-pyridyl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7,9,13-trimethyl-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadeca-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-7-ethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-10-ethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-7,9,13-trimethyl-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10,12,16-trimethyl-8,8(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] heptadeca-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-7-ethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-10-ethy(-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-enel-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-7,9,13-trimethyl-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-deca-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-7-ethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-10-ethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-7(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-7,9,13-trimethyl-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-deca-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-7-ethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-10-ethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo[14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo[14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.O] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,l3-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.O] heptadecane-5,9-

dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.O] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazoly (ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.O) heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-in-1yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)7-(prop-2-ine-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)

ethenyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-timethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(but-2-ine-1yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-

10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(but-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(11-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ine-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-5-benzoxazolyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.

(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ine-1-yl-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-1-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ine-1yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ene-1-yl)-1-aza-10 oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo-[14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,SS,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ine-1yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-

ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-5-benzothiazolyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [141.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ine-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-14,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-

benzothiazolyl)-7-(but-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzethiazolyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ine-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo (14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzo thiazolyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene-)4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-chloro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-13-chloro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-fluoro-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-fluoro-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-

thiazolyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-allyl-13-chloro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-chloro-16-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-enee-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,1OR,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-trimethylene-1,10-dioxa-7,9-dimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-trimethylene-1,10-dioxa-7,9-dimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-(chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-oxazolyl) enyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-2-pyridyl)

ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-7-ethyl-13-chloro-16-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-(chloro-7,11-dihydroxy-7-ethyl-3-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-7-ethyl-3-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-7-ethyl-13-chloro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-7-allyl-13-chloro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,1OR,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-

tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa 5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-chloro-1(3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-13-chloro-1(3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-fluoro-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-fluoro-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-allyl-13-chloro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-chloro-16-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,1OR,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl)

ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-trimethylene-1-aza-10-oxa-7,9-dimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,SS,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-trimethylene-1-aza-10-oxa-7,9-dimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-59-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-7-ethyl-13-chloro-16-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-7-ethyl-3-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-7-ethyl-3-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,1OR,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-

tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-7-ethyl-13-chloro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-7-allyl-13-chloro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl(-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.

[0012] The presentation of the new epothilone derivatives, in which R^5 is not halogen or cyano, is based on the linking of three partial fragments A, B and C. The interfaces are located at the points shown in the general formula I'.

/formula/

A is a C_1-C_6 fragment (epothilone counting method) of the general formula A-1 or A-2.

/formula/ **A1**

or

/formula/ **A2**

where
$R^{1a'}$, $R^{1b'}$, $R^{2a'}$ and $R^{2b'}$ have the meaning indicated already for R^{1a}, R^{1b}, R^{2a} and R^{2b} and
R^{19} is CH_2OR^{19a}, CH_2-hal, CHO, CO_2R^{19b}, COhal,
R^{20} is hydrogen, OR^{20a}, hal, OSO_2R^{20b},
R^{19a}, R^{20a} stands for hydrogen, SO_2-alkyl, SO_2-aryl, SO_2-aralkyl or together a $-(CH_2)_0$ group or together a
$CR^{23a}R^{23b}$ group,
R^{19b}, R^{20b} is hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl,
R^{23a}, R^{23b} are identical or different and hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together a $-(CH_2)_q$ group,
o is 2 to 4,
q is 3 to 6,
R^{21} is hydrogen,
R^{22} is hydroxyl, or
R^{21}, R^{22} together are an oxygen atom, or a C_2-C_{10} alkylene-α,ω-dioxy group which may be linear or branched.
R^{21}, R^{22} are each C_1-C_{10} alkoxy groups,
including all stereo isomers as well their mixtures as well as
free hydroxyl groups in R^{19}, R^{20} and R^{22} etherified or esterified, free carbonyl groups ketal-treated in A-1 or A-2, transferred into an enol ether or reduced as well as free acid groups in A-1 or A-2, into which salts with bases may have been transferred.

[0013] B stands for a C_7-C_{12} fragment (epothilone counting method) of the general formula

/formula/

where
$R^{3a'}$, $R^{4'}$ and $R^{5'}$ have the meaning indicated already for R^{3a}, R^4 and R^5 (with the exception of $R^{5'}$ = hal, CN) and V stands for an oxygen atom, two alkoxy groups OR^{23}, a C_2-C_{10} alkylene-α, ω-dioxy group which can be linear or branched or H/OR^{24},
W is an oxygen atom, two alkoxy groups OR^{25}, a C_2-C_{10} alkylene-α, ω-dioxy group which can be linear or branched or H/OR^{26},
R^{24}, R^{26} hydrogen independent of each other or a protection group PG^{24},
R^{23}, R^{25} stand for C_1-C_{20} alkyl independent of each other.
C stands for a C_{13}-C_{16} fragment (epothilone counting method) of the general formula

/formula/

where
G' represents a group

/formula/

a bicyclic or tricyclic aryl rest,
R^{12} has the meaning indicated already in the general formula I for R^{12} and
R^{7} is a hydrogen atom,
R^{27} is halogen, N_3, NHR^{29}, a hydroxy group, a protected hydroxy group O-PG^{27}, a protected amino group $NR^{29}PG^{27}$, a C_1-C_{10} alkyl sulfonyloxy group which may be perfluorinated, a benzoyloxy group possibly substituted with C_1-C_4 alkyl, nitro, chlorine or bromine, an $NR^{29}SO_2CH_3$ group, a $NR^{29}C(=O)CH_3$ group, a CH_2-C(=O)-CH_3 group,
R^{28} is a hydroxy group, halogen, a protected hydroxy group OPG^{28}, a phosphonium halogenoid rest $PPh_3^+hal^-$ (Ph = phenyl); hal = F, Cl, Br, I), a phosphonate rest $P(O)(OQ)_2$(Q=C_1-C_{10} alkyl or phenyl) or a phosphine oxide rest $P(O)Ph_2$(Ph = phenyl),
X is an oxygen atom, two alkoxy groups $OR^{13'}$, a C_2-C_{10} alkylene-α, ω-dioxy group which can be linear or branched or H/$OR^{14'}$ or a grouping $CR^{15'}R^{16'}$,
where,
$R^{13'}$ represents a C_1-C_{20} alkyl rest,
$R^{14'}$ stands for hydrogen or a protection group PG^{14},
$R^{15'}$, $R^{16'}$ are identical or different and stand for hydrogen, a C_1-C_{20} alkyl rest, aryl rest, C_7-C_{20} aralkyl rest,

[0014] The preparation of the new epothilone derivatives, in which R^5 is equal to halogen or cyano, is based on the cross linkage of two partial fragments A and D. The interfaces are indicated in general formula I".

/formula I"/

[0015] In that connection, A corresponds to the already described C_1-C_6 fragment (epothilone counting method) of the general formula A-1 or A-2.

[0016] D stands for a C_7-C_{15} fragment (epothilone counting method) of the general formula

/formula/

where
$R^{5"}$ stands for halogen or cyano and $R^{3a"}$, $R^{4"}$ and $R^{27"}$ and G have the meaning indicated already for R^{3a}, R^4 and R^{27} and G.

[0017] The alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^4, R^5, R^9, R^{12}, R^{13}, $R^{13'}$, R^{15}, $R^{15'}$, R^{16}, $R^{16'}$, R^{19b}, R^{20b}, R^{23}, R^{25} may consist of linear or branched alkyl groups with 1-20 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, isopentyl, neopentyl, heptyl, hexyl, decyl. The alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^4, R^5, R^9, R^{12}, R^{13}, $R^{13'}$, R^{15}, $R^{15'}$, R^{16}, $R^{16'}$, R^{19b}, R^{20b}, R^{23}, R^{23a}, R^{23b}, R^{25} may be perfluorinated or substituted with 1-5 halogen atoms, hydroxy groups, C_1-C_4 alkoxy groups, C_6C_{12} aryl groups (which may be substituted with 1-3 halogen atoms).

[0018] The aryl rests R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^4, R^5, R^9, R^{12}, R^{15}, $R^{15'}$, R^{16}, $R^{16'}$, R^{19b}, R^{20b}, R^{23a},

R^{23b} may consist of substituted and non-substituted carbocyclic or heterocyclic rests with one or morel hetero atoms such as phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, chinolyl, thiazolyl, benzothiazolyl, benzo-oxazolyl which may be substituted once or several times with halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy groups.

[0019] Bicyclic and tricyclic aryl rests G may consist of substituted and non-substituted carbocyclic or heterocyclic rests with one or more hetero atoms such as naphthyl, anthryl, benzothiazolyl, benzo-oxazolyl, benzimidazolyl, chinolyl, isochinolyl, benzo-oxazinyl, benzofuran, indolyl, indazolyl, chinoxalinyl, tetrahydro-isochinolinyl, tetrahydro-chinolinyl, thienopyridinyl, pyridopyridinyl, benzopyrazolyl, benzotriazolyl, dihydroindolyl which may be substituted once or more times with halogen, OH, O-alkyl, CO_2H, CO_2 alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl, C_1-C_{20}-acyloxy groups.

[0020] The aralkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^4, R^5, R^9, R^{12}, R^{15}, $R^{15'}$, R^{16}, $R^{16'}$, R^{19b}, R^{20b}, R^{23a}, R^{23b} may have up to 14 C-atoms and preferably 6 to 10 atoms in the ring and between 1 and 8 atoms and preferably between 1 and 4 atoms in the alkyl chain. Aralkyl rests may consist of benzyl, phenyl ethyl, naphthyl methyl, naphthyl ethyl, furyl methyl, thienyl ethyl, pyridyl propyl. The rings may be substituted once or more times with halogen, OH, O-alkyl, CO_2H, CO_2 alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20} alkyl, C_1-C_{20} acyl, C_1-C_{20} acyloxy groups.

[0021] The alkoxy groups contained in R^{21}, R^{22} and X of general formula I should have between 1 and 20 carbon atoms, in which case preference is given to methoxy, ethoxy, propoxy, isopropoxy and t-butyloxy groups.

[0022] Representatives of the protection groups PG consist of alkyl- and/or aryl-substituted silyl, C_1-C_{20} alkyl, C_4-C_7 cycloalkyl which may have an additional oxygen atom in the ring, aryl, C_7-C_{20} aralkyl, C_1-C_{20} acyl as well as aroyl.

[0023] Alkyl rests, silyl rests and acyl rests for the protection groups PG may consist of rests that are known to the expert. Among the respective alkyl ethers and silyl ethers, preference is given to the alkyl rests or silyl rests that are easy to separate such as the following rests: methoxy methyl, methoxy ethyl, tetrahydro pyranyl, tetrahydro furanyl, trimethyl silyl, triethyl silyl, tert. butyl dimethyl silyl, tert. butyl diphenyl silyl, tribenzyl silyl, triisopropyl silyl, benzyl, para-nitrobenzyl, para-methoxy benzyl as well as alkyl sulfonyl rests and aryl sulfonyl rests. Acyl rests may consist of formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl which may be substituted with amino groups and/or hydroxy groups.

[0024] Rests known to the expert can be used as amino protection groups. Rests mentioned here as examples include the groups alloc, boc, Z, benzyl, f-moc, troc, stabase or benzostabase.

[0025] The acyl groups PG may contain between 1 and 20 carbon atoms, in which case the formyl, acetyl, propionyl, isopropionyl and pivalyl groups are preferred.

[0026] Index m of the alkylene group formed from R^{1a} and R^{1b} preferably stands for 1, 2, 3 or 4.

[0027] The C_2-C_{10} alkylene-α, ω-dioxy group possible for R^{21}, R^{22}, V, W and X preferably consists of an ethylene ketal or neopentyl ketal group.

Preparation of partial fragments A

[0028] The partial fragments (synthesis modules) of the general formula A-1 and A-2 can be prepared as described in DE 197 51 200.3, DE 199 07 480.1, DE 19 92 861.1 and WO 99/07692.

Preparation of partial fragments B
Schematic representation 1

/formula/

[0029] The preparation of fragments of the type B, in which $R^{3a'}$, $R^{4'}$, $R^{5'}$, V and W may have all of the meanings indicated above, is shown in schematic representation 1. The synthesis can be performed on the basis of enantiomer-pure compounds B-I as well as in a racemic manner.

Step a (B-I -> B-II)

[0030] Some of the compounds of type B-I are commercially available. In these cases, the primary alcohol function is selectively protected with methods known to the expert. For example, it is basically possible to consider all protection groups named for PG^5. Particular preference is given to the protection group "tetrahydro pyranyl". To obtain compounds of the type B-I that are not commercially available, the rest $R^{4'}$ is prepared with methods known to the expert, e.g., with a nucleophilic substitution on a corresponding aldehyde.

Step b (B-II -> B-III)

[0031] Compounds of the type B-II are obtained with a 1,4-addition of compounds of the type B-II on α,ß-unsaturated carbonyl compounds. In that connection, $R^{5'a}$ may have all meanings mentioned already for $R^{5'}$ and may also stand for O-alkyl.

Step c (B-III -> B-IV)

[0032] Compounds of the type B-III, in which $R^{5'a}$ stands for O-alkyl, can be reduced to form aldehyde B-IV. The transformation to aldehyde occurs either in a direct manner by way of a reduction with diisobutyl aluminum hydride at low temperatures (less than -40 °C) or in two stages by a reduction to alcohol and a subsequent oxidation. This can be achieved with methods that are known to the expert. The reduction may be performed with complex hydrides such as lithium aluminum hydride. The oxidation may be achieved with the method described for the preparation of A-III.

Step d (B-IV -> B-V)

[0033] A nucleophilic addition of metal-organic compounds of the theoretical formula $M\text{-}R^{5'}$, in which M stands for indium, an alkali metal and preferably for lithium or a bivalent metal MX, in which X represents a halogen and the rest $R^{5'}$ has the above-mentioned meaning. The preferred bivalent metal is magnesium and zinc and halogen X preferably consists of chlorine, bromine or iodine.

Step e (B-III -> B-V)

[0034] With compounds in which $R^{5'a}$ stands for O-alkyl, it is also possible to obtain compounds of the type B-V directly through a nucleophilic addition. This is achieved with methods that are known to the expert such as the use of dialkyl copper lithium compounds.

Step f (B-V -> B)

[0035] The transformation of B-V into partial fragments of the general formula B is realized as described in WO 99/07692.

Step g (B-III -> B)

[0036] For compounds, in which $R^{5'a}$ does not stand for O-alkyl, compound B-III can also be transformed to partial fragments of the type B analogous to WO 99/07692.

Preparation of partial fragments C

[0037] The partial fragments (synthesis modules) of the general formula C can be prepared as indicated in DE 197 51 200.3, DE 199 07 480.1 and WO 99/07692.

[0038] The preparation of partial fragments ABC and their cyclicizing to I is also achieved as described in WO 99/07692 for many epothilone derivatives; WO 99/07692 demonstrates already the general applicability of the synthesis principle described in the following for the compounds in accordance with the invention. Furthermore, WO 99/07692 yields many synthesis modules of the general formula A, B and C, with which it is possible to obtain other compounds of the general formula I claimed here. Synthesis modules of the general formula C, in which R^{12} consists of a halogen atom and particularly of a fluoride, chlorine or bromine atom, form the object of DE 199 07 480.1 and PCT/EP00/01333.

Preparation of partial fragments D

[0039] The synthesis of partial fragments D is described in the following schematic representation 2 on the bases of the aldehydes of the general formula D-I.

/Schematic representation 2/

Step a (D-I -> D-IV)

[0040] The compound D-I is alkylized with the enolate of a carbonyl compound of the general formula D-II, in which X represents a hydrogen and chG^2 a chiral auxiliary group, using the methods which are known to the expert. The enolate is prepared using strong bases such as lithium diisopropyl amide, lithium hexamethyl disilazane at low temperatures. Another possibility consists in the use of a Reformatzsky reaction, in which the compound of the general formula D-II with X = halogen and preferably chlorine or bromine is transformed with $CrCl_2$ into a metallo-organic reagent that is then reacted with the aldehyde D-I to form D-IV. As chiral auxiliary group chG^2-H (D-III) are suitable chiral and inexpensive alcohols that can be manufactured in an optically pure manner such as pulegol, 2-phenyl cyclohexanol, 2-hydroxy-1,2,2-triphenyl ethanol, 8-phenyl

menthol or compounds that contain inexpensive, reactive NH groups that can be manufactured in an optically pure manner such as amine, amino acid, lactam or oxazolidinone. Preference is given to oxazolidinone and particular preference to compounds of the formulas D-IIIa to D-IIId. The absolute stereo-chemistry on the α-carbonyl carbon of the general formula D-IV is established with the selection of the respective antipode. In that manner, it is possible to obtain the compounds of the general formula D-IV to D-XV or their respective enantiomers ent-D-IV to ent-D-XV in an enantiomer-free manner. When the chG^2-H (D-III) is replaced with an achiral alcohol such as ethanol, one obtains the racemic compounds rac-D-IV to rac-D-XV.

[0041] The free hydroxyl group in B-IV is then protected using the methods known to the expert. As protection groups PG15, one can consider the same protection groups that were indicated earlier for PG5 (A-I -> A-II) and are known to the expert.

[0042] Preference is given to silicon-containing protection groups that can be cracked under acid reaction conditions or with the use of fluoride such as the rests trimethyl silyl, triethyl silyl, tert.-butyl dimethyl silyl, tert.-butyl diphenyl silyl, tribenzyl silyl and triisopropyl silyl.

[0043] Particularly preferred is tert.-butyl diphenyl silyl and tert. butyl dimethyl silyl rest.

Step b (D-IV -> D-V)

[0044] When the group chG^2 represents one of the chiral auxiliary groups mentioned in step a, it will be recovered with a transesterification of D-IV in an alkyl ester of the general formula D-V. The transesterification is achieved with methods that are known to the expert. Preference is given to a transesterification with simple alcohols such as methanol or ethanol in the presence of the respective titanium(IV) alcoholates.

Step c (D-V -> D-VI)

[0045] The ester in D-V is reduced to the alcohol D-VI. Suitable reduction agents that are known to the expert consist of aluminum hydride such as lithium aluminum hydride or diisobutyl aluminum hydride. The reaction is performed in an inert solvent such as diethyl ether, tetrahydrofuran or toluene.

Step c' (D-IV -> D-VI)

[0046] As an alternative to steps b) and c), the carbonyl group in D-IV can be reduced directly to alcohols of the general formula D-VI under the conditions mentioned in step c). The chiral auxiliary components chG^2-H can be recovered here as well.

Step d (D-VI -> D-VII)

[0047] The oxidation of the primary alcohol in D-VI to form aldehyde of the general formula D-VII is achieved with methods that are known to the expert. Mentioned here as examples are an oxidation process with pyridinium chlorochromate, pyridinium dichromate, chromotrioxide pyridine complex, oxidation processes according to Swern or similar methods such as a use of SO_3

pyridine complex or oxalyl chloride in dimethyl sulfoxide, the use of the Dess-Martin periodinans, the use of nitrogen oxides such as N-methyl morpholino-N-oxide in the presence of suitable catalysts such as tetrapropyl ammonium perruthenate in inert solvents. Preference is given to an oxidation by Swern, with SO_3-pyridine complex as well as with N-methyl morpholino-N-oxide with the use of tetrapropyl ammonium perruthenate.

Step e (D-VII -> D-VIII)

[0048] The unsaturated esters of the general formula D-VIII are prepared with methods known to the expert. Suitable methods consist of the Wittig or Wittig/Horner reaction as well as the Peterson olefin process. Preference is given to the Wittig/Horner reaction with the use of phosphonates of the type alkylOOC-CHR^{5n}-$P(O)(OAlkyl')_2$, in which case alkyl and alkyl' can be identical or different and preferably indicate methyl, ethyl, i-propyl or trifluoro ethyl and $R^{5'}$ has the meaning given earlier, with bases such as potassium carbonate, sodium hydride, n-butyl lithium, potassium-tert.-butanolate, sodium methanolate, lithium hexamethyl disilazane, sodium hexamethyl disilazane, potassium hexamethyl disilazane and possibly with additives such as Krone (crown) ethers, DMPU or HMPA in solvents such as methanol, tetrahydrofuran dimethyl formamide, diethyl ether and preference is given to a combination of potassium carbonate in methanol, sodium hydride in dimethyl formamide or tetrahydrofuran and potassium hexamethyl disilazane with 18-Krone(crown)-6 in tetrahydrofuran.

[0049] The obtained E/Z diastereomers may be separated in this or the next phase and may be transformed individually to form the respective E- or Z-olefin products. The schematic formula representation shows only the E-form for the sake of clarity. However, all following steps apply for the respective Z-isomer as well.

Step f (D-VIII -> D-IX)

[0050] Compounds of the type D-VIII are transformed to compounds of the type D-IX by way of a C_1-extension. This C_1-extension is achieved using multi-stage methods. It is possible, for example, to reduce the ester function in D-VIII to a primary alcohol. Suitable reducing agents that are known to the expert consist of aluminum hydride such as lithium aluminum hydride or diisobutyl aluminum hydride. The reaction takes place in an inert solvent such as diethyl ether, tetrahydrofuran and toluene. The primary alcohol can then be transformed to a volatile group such as a halogenoid or an OSO_2 alkyl, O-SO_2 aryl or OSO_2 aralkyl group. The introduction of the later C-14 can the be achieved, for example, through a substitution with cyanide with the use of NaCN or KCN. The nitrile thus formed is then transformed by way of a reduction with diisobutyl aluminum hydride and an acid fission of the primarily formed imine to form an aldehyde that can then be transformed to the primary alcohol of the type D-IX with lithium aluminum hydride, sodium borohydride or diisobutyl aluminum hydride.

Step g (D-IX + B-II -> D-X)

[0051] The preparation of compounds of the type D-X is then achieved by linking D-IX with the already-described compounds of the type B-II. This may be done with the use of triphenyl phosphine and azodiester such as azodicarbonic acid diethyl ester. As an alternative, one of the two

hydroxy functions (in module D-IX or B-II) can be transformed into a halogenoid or an OSO_2 alkyl, OSO_2 aryl or OSO_2 aralkyl group. The volatile group is preferably formed on the primary alcohol function in module D-IX. To link the two modules, the free hydroxyl group is then de-protonated in the respective other module and preferably B-II with suitable bases such as sodium hydride, n-butyl lithium, 4-dimethyl aminopyridine, Hünig base, alkylihexamethyl disilazanes and are then transformed through a nucleophilic substitution in compounds of the type D-X.

Step h (D-X -> D-XI)

[0052] For the case $R^{27} = OPG^{27'}$, the protection group PG^7 will now be separated using methods that are known to the expert. In the case of a protection group that can be separated in an acid form, the separation can be achieved with diluted mineral acids in aqueous-alcoholic solutions, with the use of catalytic quantities of acids such as para-toluene sulfonic acids, para-toluene sulfonic acid pyridinium salt, camphor sulfonic acid in alcoholic solutions and preferably in ethanol or isopropanol.

[0053] When A is a NR^{17}-group in the compounds of formula I, protection group PG^{27} is separated first and selectively with methods known to the expert, i.e., prior to the separation of protection group PG^7 (see also above). The secondary alcohol thus obtained is - by way of a sulfonyl chloride or a sulfonic acid anhydride - transformed to a sulfonate and is then possibly in a Finkelstein reaction using an alkali bromine or chloride or by reacting the secondary alcohol with CBr_4 in the presence of triphenyl phosphine or bis(diphenyl phosphine ethane) transformed to a secondary halogenoid. The halogenides or sulfonates thus obtained can then be transformed by way of a nucleophilic substitution with sodium azide in a neutral polar solvent such as dimethyl formamide or dimethyl sulfoxide to form a corresponding azide ($L' = N_3$). This would then be followed by the above-described fission of protection group PG^7.

Step i (D-XI -> D)

[0054] The oxidation of the primary alcohol in D-XI to form the corresponding aldehyde is achieved with methods that are known to the expert. As examples shall be named an oxidation with pyridinium chlorochromate, pyridinium dichromate, chromotrioxide pyridine complex, an oxidation according to Swern or related methods such as the use of a SO_3-pyridine complex or of oxalyl chloride in dimethyl sulfoxide, the use of the Dess-Martin periodinans, the use of nitrogen oxides such as N-methyl-morpholino-N-oxide in the presence of suitable catalysts such as tetrapropyl ammonium perruthenate in inert solvents. Preference is given to an oxidation by Swern as well as an oxidation with N-methyl morpholino-N-oxide with the use of tetrapropyl ammonium perruthenate.

[0055] When $R^{3a''}$ is not equal to H, the respective secondary alcohol can now be prepared - using methods that are known to the expert - with metal-organic compounds of the general formula $M-R^{3a''}$, where M indicates an alkali metal and preferably lithium or a bivalent metal MX, where X represents a halogen and rest $R^{3a''}$ has the above-mentioned meaning. The bivalent metal preferably consists of magnesium and zinc and the halogen X preferably consists of chlorine, bromine or iodine.

[0056] The secondary alcohol thus obtained is by way of an oxidation transformed to the ketone of the general formula D with R3' not equal to H using the methods listed earlier in i). Preference is given to an oxidation with N-methyl morpholino-N-oxide with the use of tetrapropyl ammonium perruthenate.

Partial fragments of the general formula AB

/formula/

AB-1 **or** **AB-2**

where $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, $R^{3a'}$, $R^{4'}$, $R^{5'}$, R^{19}, R^{20}, R^{21}, R^{22}, V and Z have the earlier-mentioned meanings and PG^7 is a hydrogen atom or a protection group PG, are obtained from the above-mentioned fragments A and B using the method shown in schematic representation 3.

Schematic representation 3

/formulas/

Step aa (A + B -> AB)

[0057] Compound B, in which W stands for an oxygen atom and possibly for existing additional carboxyl groups are protected, is alkylized with the enolate of a carboxyl compound of the general formula A. The enolate is prepared under the effects of strong bases such as lithium diisopropyl amide, lithium hexamethyl disilazane at low temperatures.

Partial fragments of the general formula BC

/formula/

where $R^{3a'}$, $R^{4'}$, $R^{5'}$, R^6, R^7, R^{27}, G and W have the earlier-mentioned meanings, are obtained from the above-described fragments B and C using the method shown in schematic representation 4.

Schematic representation 4

/formulas/

Step ab (B + C -> BC)

[0058] Compound C, in which R^{28} indicates a Wittig salt and possibly present additional carbonyl groups are protected, is de-protonated with a suitable base such as n-butyl lithium, lithium diisopropyl amide, potassium tert.-butanolate, sodium- or lithium-hexamethyl disilazide and is reacted with a compound B, where V indicates oxygen and W stands for two alkoxy groups OR^{25}, a C_2-C_{10}-alkylene-$\alpha\omega$-dioxy group that can be linear or branched or may have H/OR^{26}.

Partial fragments of the general formula ABC (AB + C)

/formulas/

where $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, $R^{3a'}$, $R^{4'}$, $R^{5'}$, R^{6}, R^{7}, R^{19}, R^{20}, R^{21}, R^{22}, G' and Z have the earlier-mentioned meanings and PG^{7} is a hydrogen atom or a protection group PG, are obtained from the above-described fragments AB and C using the method shown in schematic representations 5 and 6.

Schematic representation 5

/formulas/

Step ac (AB+ -> ABC)

[0059] Compound C, in which R^{28} indicates a Wittig salt and possibly present additional carbonyl groups are protected, is de-protonated with a suitable base such as n-butyl lithium, lithium diisopropyl amide, potassium tert.-butanolate, sodium- or lithium-hexamethyl disilazide and is reacted with a compound AB, where V indicates an oxygen atom.

Schematic representation 6

/formulas/

Step ad (A + BC -> ABC)

[0060] Compound BC, in which W represents an oxygen atom and in which additional and possibly present carbonyl groups are protected, is alkylized with the enolate of a carbonyl compound of the general formula A. The enolate is prepared under the effects of strong bases such as lithium diisopropyl amide or lithium hexamethyl disilazane at low temperatures.

Preparation of partial fragments AD

Partial fragments of the general formula AD

/formulas/

where $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, $R^{3a'}$, $R^{4'}$, $R^{5''}$, R^{19}, R^{20}, $R^{27'}$, G'' and Z have the earlier-mentioned meanings are obtained from the above-described fragments A and D using the method shown in schematic representations 7.

Schematic representation 7

/formulas/

Step a (A + D -> AD)

[0061] Compound D is alkylized with the enolate of a carbonyl compound of the general formula A. The enolate is prepared under the effects of strong bases such as lithium diisopropyl amide or lithium hexamethyl disilazane at low temperatures.

[0062] The transformation of fragments ABC or AD to compounds of the general formula I is achieved with the methods described in the following. The only difference between fragments ABC and AD consists in the fact that rest $R^{5'}$ can have all meanings of R^5 in fragments ABC - with the exception of halogen and cyano - and $R^{5''}$ stands for halogen and cyano in fragments AD.

Step ae (ABC-1 or AD-1 -> I)

[0063] Compounds ABC-1 or AD-1, in which R^{19} represents a carbonic acid CO_2H and R^{27} a hydroxyl group or an amino group, are reacted with methods known to the expert for the formation of large macrolides or macrolactams to form compounds of the formula I, in which A-Y stands for a O-(C=O) group or NR^{29}-C(C=O) group. The formation of lactone is preferably achieved with the method described in "Reagents for Organic Synthesis, Vol. 16, Page 353" using 2,4,6-trichlorobenzoic acid chloride and suitable bases such as triethyl amine, 4-dimethyl amino pyridine and sodium hydride. The formation of lactam is preferably achieved with a reaction of the amino acid (R^{19} is a carbonic acid CO_2H and R^{27} is a NHR^{29} group) with diphenyl phosphoryl azide in the presence of a base.

Step af (ABC-1 or AD-1 -> I)

[0064] Compounds ABC-1 or AD-1, in which R^{19} represents a group CH_2OH and R^{27} a hydroxyl group, are preferably and with the use of triphenyl phosphine and azodiesters such as azodicarbonic acid reacted to form compounds of formula I, in which A-Y represents an O-CH_2 group.

[0065] Compounds ABC or AD, in which R^{19} represents a group CH_2-Hal or CH_2OSO_2-alkyl or CH_2OSO_2 aryl or CH_2OSO_2 aralkyl and R^{27} represents a hydroxyl group, can - after the de-protonating - undergo a cyclicizing with suitable bases such as sodium hydride, n-butyl lithium, 4-dimethyl aminopyridine, Hünig base, alkyl hexamethyl disilazane to form compounds of formula I, in which A-Y has the meaning of an O-CH_2 group.

Step ag (ABC-2 or AD-2 -> I)

[0066] Compounds ABC-2 and AD-2, in which R^{21} and R^{22} jointly represent an oxygen atom and R^{27} is a $NR^{29}SO_2$-CH_3 group can undergo a cyclicizing under the effects of strong bases such as lithium diisopropyl amide and lithium hexamethyl disilazane at low temperatures to form sulfonamide I, in which A-Y stands for an $NR^{29}SO_2$ group.

Step ah (ABC-2 or AD-2 -> I)

[0067] Compounds ABC-2 and AD-2, in which R^{21} and R^{22} jointly represent an oxygen atom and R^{27} an O-C(=O)CH_3 group can undergo a cyclicizing under the effects of strong bases such as lithium diisopropyl amide and alkali hexamethyl disilazane at low temperatures to form lactone I, in

which A-Y stands for an O-C(=O)-group.
Step ah (ABC-2 or AD-2 -> I)

[0068] Compounds ABC-2 and AD-2, in which R^{21} and R^{221} jointly represent an oxygen atom and R^{27} a $CH_2C(=O)CH_3$ group, can undergo a cyclicizing under the effects of strong bases such as lithium diisopropyl amide and alkali hexamethyl disilazane at low temperatures to form lactone I, in which A-Y stands for a $CH_2C(=O)$-group.

Introduction of the nitrogen function for R^{27}

[0069] The amino group NHR^{29} can be introduced at the stage of the C-fragment, the BC-fragment or of the ABC-fragment using methods that are known to the expert. Preference is given to a preparation from the azide (R^{27} =N_3) that was transformed using methods known to the expert and preferably with the use of a phosphine such as triphenyl phosphine in the presence of water to form the amine (R^{27} = NHR^{29}) that should be protected, if possible, for the further reaction progress. The azide introduction can be achieved using the Mitsunobu reaction in the presence of metal azides and preferably sodium or zinc azide or by a substitution of a suitable loss group such as a chlorine, bromine or iodine atom, an alkyl sulfonyloxy group, a perfluorated alkyl sulfonyloxy group or aryl sulfonyloxy group or aralkyl sulfonyloxy group through azides.

[0070] The flexible functionalization of the described modules A, B and C also ensures a linkage sequence that differs from the above-described methods and that leads to modules ABC. These methods are summarized in the following table:

Linkage possibilities	Linking methods a through e	Preconditions
A + B -> A-B	a: Aldol (see schematic representation 3)	Z = W = Oxygen
B + C -> B-C	b: Wittig (see schematic representation 4) e: McMurry	U = oxygen and R^{28} = Wittig salt, phosphine oxide or phosphonate U = V = oxygen
A + C -> A-C	c: Esterification (e.g. 2,4,6-trichloro benzoyl chloride and 4-dimethyl aminopyridine) d: Etherification (e.g., according to Mitsunobu) f: Amide formation (e.g., with $(PhO)_2P(O)N_3$) in the presence of a base in an inert solvent) g: Ketone formation through a aldol reaction with a strong base. h: Sulfonamide formation in the presence of a strong base.	R^{19} =CO_2R^{19b} or CoHal and R^{27} = hydroxyl R^{19} = CH_2OH and R^{27} = hydroxyl or OSO_2-alkyl or OSO_2-aryl or OSO_2-aralkyl R^{19} = CO_2R^{19b} or CoHal and R^{27} = NHR^{29} R^{27} = $CH_2C(=O)CH_3$ and R^{21}, R^{22} = oxygen R^{27} = $NR^{29}SO_2CH_3$ and R^{21}, R^{22} = oxygen R^{27} = $NR^{29}C(=O)CH_3$ and R^{21}, R^{22}

	i: Amide formation in the presence of a strong base.	= oxygen

[0071] Modules A, B and C can be linked with these methods as shown in schematic representation 10.

Schematic representation 10

/formulas/ oder = or

[0072] A further functional change can be achieved for free hydroxyl groups in I, A, B, C, AB, BC, ABC with an etherification or esterification and for free carbonyl groups with a ketalization, formation of enol ether or a reduction.

[0073] The invention concerns all stereoisomers of these compounds and also their mixtures.

[0074] The invention also concerns all pro-drug formulations of these compounds, i.e., all compounds that release a bio-active substance of the general formula I in vivo.

Biological effects of and application ranges for the new derivatives

[0075] The new compounds of Formula I are valuable pharmaceutical products. They interact with tubuline by stabilizing the formed micro-tubulines and they are thus capable of affecting the cell division in a phase-specific manner. This applies particularly to fast-growing neoplastic cells, whose growth remains mostly unaffected by inter-cellular control mechanisms. Substances of that type can basically be used to treat malignant tumors. The possible application range includes the therapy for ovarian carcinoma, gastric c., colon c., adenocarcinoma, breast c., pulmonary carcinoma, head c. and neck c., malignant melanoma, acute lymphocytic and myelocytic leukemia. Furthermore and based on their properties, the compounds in accordance with the invention can be used for the anti-angiogenesis therapy as well as to treat chronic inflammatory diseases such as psoriasis, multiple sclerosis and arthritis. To prevent an uncontrollable cell proliferation on medical implants as well as to improve the compatibility of medical implants, they can basically be applied on or in the polymeric materials to be utilized. The compounds in accordance with the invention can be used alone or - to achieve cumulative or synergistic effects - in combination with other principles and substance classes utilized for the tumor therapy.

[0076] The following combinations shall be listed as examples:

- Platinum complexes such as cisplatine and carboplatine.
- Intercalating substances like those from the class of anthracyclines such as doxorubicine or those from the class of anthrapyrazoles such as CI-941.
- Substances that interact with tubuline like those from the class of the Vinca-alkaloids such as vincristine, vinblastine or from the class of taxanes such as taxol, taxoter or those from the class of macrolides such as rhizoxin or other compounds such as colchicine, combretastine A-4, discodermolide and its analogs.
- DNA-topoisomerase-inhibitors such as camptothecine, etoposide, topotecane, teniposide.
- Folate- or pyrimidine-antimetabolites such as lometrexol, gemcitubine.

- DNA-alkylizing compounds such as adozelesine, dystamycine A.
- Inhibitors of growth factors (e.g., of PDGF, EGF, TGFb, EGF) such as somatostatine, suramin, bombesine-antagonists.
- Inhibitors of the protein tyrosine kinases A or C such as erbstatine, genistein, staurosporine, ilmofosine, 8-CI-cAMP.
- Antihormones from the class of the antigestagines such as mifepristone, onapristone or from the class of the anti-estrogens such as tamoxifene or from the class of the anti-androgens such as cyproterone acetate.
- Metastasis-inhibiting compounds like those from the class of eicosanoides such as PGI_2, PGE_1, 6-oxo-PGE_1 as well as their stable derivatives (e.g., iloprost, cicaprost, misoprostol).
- Inhibitors for oncogenic RAS-proteins that affect the mitotic signal transduction such as inhibitors of the farnesyl-protein-transferasis.
- Natural or man-made antibodies such as erbB2-antibodies prepared to work against factors or their receptors that promote tumor growth.

[0077] The invention also concerns drugs on the basis of pharmaceutically compatible compounds of the general formula I, i.e., compounds without a toxic effect in the given dosage, possibly together with commonly used auxiliary and carrier substances.

[0078] The compounds in accordance with the invention can be encapsuled with liposomes or enclosed in an α-, ß- or γ-cyclodex trinclathrate.

[0079] The compounds in accordance with the invention can be processed to form pharmaceutical preparations for an enteral, percutane, parenteral or local application using methods that are generally known in the field of galenism. They can be administered in the form of tablets, coated tablets, gel capsules, granulates, suppositories, implants, injectable sterile aqueous or oily solutions, suspensions or emulsions, ointments, cremes and gels.

[0080] In that regard, the active substance or substances may be mixed with auxiliary substances that are generally known in the field of galenism such as gum arabic, talc, starch, mannite, methyl cellulose, lactose, tensides such as tweens or myrj, magnesium stearates, aqueous or non-aqueous carriers, paraffin derivatives, netting-, dispersing-, emulsifying- and conserving agents and aroma substances to affect the taste (e.g., etheric oils).

[0081] Accordingly, the invention also concerns pharmaceutical compositions that contain at least one compound in accordance with the invention as an active substance. A dosage unit contains approx. 0.1 - 100 mg of the active substance(s). For humans, the compounds in accordance with the invention are administered at dosages of 0.1 - 1000 mg per day.

[0082] The following examples serve to explain the invention in more detail without restricting it:

Example 1
4S,7R,8S,9R,13(Z),16S(Z)-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,7,9,13-penta methyl cyclo-hexadec-13-ene-2,6-dione

Example 1a

(R)-1-(tetrahydro-2H-pyran-2-yl(oxy))-propane-2-ol

[0083] A solution of 5 g (65.7 mmol) R-1,2-propanediol, 6.15 ml (68 mmol) 3,4-dihydro-2H-pyran and 0.2 g p-toluene sulfonic acid-pyridinium salt in 100 ml dichloromethane was stirred for 20 hours at a temperature of 25 °C. This was then neutralized by adding triethyl amine and the reaction solution was concentrated in a vacuum. According to the column chromatography on silica gel with a mixture of ethyl acetate/hexane, one obtained 7.08 g (44.18 mmol; 67%) 1a.
^{1}H-NMR($CDCl_3$): δ = 1.13 (3H), 1.48-1.59 (4H), 1.70-1.90 (2H), 3.40-4.00 (5H) 4.55 (1H) ppm.

Example 1b
(5R)-5-methyl-4-oxa-6-(tetrahydro-2H-pyran-2-yl(oxy) hexanoic acid ethyl ester

[0084] A solution of 7.08 g (44.18 mmol) of the compound described in 1a, 95 ml (877 mmol) acrylic acid ethyl ester, 3.5 ml aqueous tetrabutyl ammonium hydroxide solution (10% 1g), 180 ml 50% aqueous sodium hydroxide solution in 300 ml toluene was stirred for 2 hours at a temperature of 25 °C. The solution was then poured on ice water. One extracted with ethyl acetate, washed the organic phase with a saturated aqueous sodium chloride solution, dried by way of sodium sulfate and concentrated in a vacuum. According to the column chromatography of the obtained raw product on silica gel with a mixture of ethyl acetate/hexane, one obtained 7.704 g (29.60 mmol; 67%) 1b.
^{1}H-NMR($CDCl_3$): δ = 1.12-1.20 (3H), 1.27 (3H), 1.48-1.90 (6H), 2.58 (2H), 3.30-4.00 (7H), 4.15 (2H), 4.60-4.70 (1H) ppm.

Example 1c
(5R)-5-methyl-4-oxa-6-(tetrahydro-2H-pyran-2-yl(oxy) hexane-1-ol

[0085] A solution of 7.704 g (29.60 mmol) 1b in 70 ml tetrahydrofuran was added in drops and at 0 °C to a suspension of 1.7 g (44.80 mmol) lithium aluminum hydride in 100 ml tetrahydrofuran. This was stirred for one hour at 0 °C and 10 ml of a saturated aqueous ammonium chloride solution was then added. This was followed by a filtering with Celite and a concentrating in a vacuum. According to the column chromatography of the obtained raw product on silica gel with a mixture of ethyl acetate/hexane, one obtained 6.204 g (28.41 mmol; 96%) 1c.
^{1}H-NMR($CDCl_3$): δ = 1.10-1.22 (3H), 1.45-1.90 (8H), 2.95 (1H), 3.30-4.05 (8H), 4.58-4.70 (1H) ppm.

Example 1d
(5R)-5-methyl-4-oxa-6-(tetrahydro-2H-pyran-2-yl(oxy) hexane-1-al

[0086] To a solution of 3.67 ml (42.62 mmol) oxalyl chloride in 100 ml anhydrous dichloromethane was added at -70 °C a solution of 5.99 ml (85.25 mmol) dimethyl sulfoxide in 10 ml dichloromethane. This was stirred for 3 minutes at -70 °C and to this was then added a solution of 6.204 g (28.41 mmol) 1c in 100 ml dichloromethane. This was stirred further for 30 minutes at -70 °C. This was then reacted with 31.5 ml (227.36 mmol) triethyl amine and was allowed to react for 30 minutes at -50 °C. The reaction mixture was then poured on an aqueous sodium hydrogen carbonate solution. This was extracted with dichloromethane. The organic phase was washed with a saturated aqueous sodium chloride solution and was dried by way of sodium sulfate. The thus

obtained raw product (6.15 g, 100%) was used in the following stage without cleaning.

Example 1e
(6R)-6-methyl-5-oxa-7-(tetrahydro-2H-pyran-2-yl(oxy) heptane-2-ol

[0087] A quantity of 19 ml (57 mmol) of a 3-molar solution of methyl magnesium chloride in tetrahydrofuran was diluted with 80 ml tetrahydrofuran. This was subsequently cooled to 0 °C and 6.15 g (28.41 mmol) of a solution of the compound described in 1d in 70 ml tetrahydrofuran was added. The mixture was stirred for 30 minutes at 0 °C and the reaction mixture was then poured on a saturated aqueous ammonium chloride solution. This was followed by an extraction with ethyl acetate. The organic phase was washed with a saturated aqueous sodium chloride solution and was dried by way of magnesium sulfate. According to the column chromatography of the obtained raw product on silica gel with a mixture of ethyl acetate/hexane, one obtained 6.008 g (25.86 mmol; 91%) 1e.
^{1}H-NMR($CDCl_3$): δ = 1.12-1.22 (6H), 1.50-1.90 (8H), 3.32-4.07 (8H), 4.58-4.69 (1H) ppm.

Example 1f
(6R)-6-methyl-5-oxa-7-(tetrahydro-2H-pyran-2-yl(oxy) heptane-2-one

[0088] A solution of 6.008 g (25.86 mmol) of the compound described in 1e, 5.38 g (46.02 mmol) N-methyl morpholino-N-oxide and 407 mg (1.16 mmol) tetrapropyl ammonium perruthenate in 200 ml dichloro methane was reacted using a molecular mesh (4A, approx. 600 spheres). This was then stirred for 20 hours at 25 °C. The mixture was concentrated in a vacuum. The thus obtained raw product was cleaned with a mixture of ethylene acetate/hexane by way of a column chromatography on silica gel. This yielded: 5.892 g (25.60 mmol: 99%) 1f.
^{1}H-NMR($CDCl_3$): δ = 1.11-1.18 (3H), 1.45-1.88 (6H), 2.18 (3H), 2.67 (2H, 3.30-3.98 (7H), 4.59-4.70 (1H) ppm.

Example 1g
(2R,6Z,9S,10Z)-2,6-dimethyl-9[[dimethyl(1,1-dimethyl ethyl) silyl] oxy]-10-fluoro-11-(2-methyl-4-thiazolyl)-3-oxa-un-deca-6,10-diene-1-ol-tetrahydropyran-2-yl-ether (A)

(2R,6E,9S,10Z)-2,6-dimethyl-9[[dimethyl(1,1-dimethyl ethyl) silyl] oxy]-10-fluoro-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-diene-1-ol-tetrahydropyran-2-yl-ether (B)

[0089] A solution of butyl lithium in hexane (3.73 ml; 9.33 mmol; 2.5 M) was added at 0 °C and in drops to a suspension of 4.498 g (7.81 mmol) (3S,4Z)-5-(2-methyl thiazol-4-yl)-3-(tert.-butyl-dimethyl silyloxy-4-fluoro-4-pentene-triphenyl phosphonium iodide in 35 ml tetrahydrofuran. The mixture was stirred for another 30 minutes and a solution of 1.5 g (6.51 mmol) of compounds described for 1f in 35 ml tetrahydrofuran was added. This was then stirred for another 3 hours at 0 °C. The reaction mixture was then poured on a saturated aqueous ammonium chloride solution. One extracted with ethyl acetate, washed the organic phase with saturated aqueous sodium chloride solution and dried by way of sodium sulfate. The thus obtained raw product was cleaned with a mixture of ethylene acetate/hexane by way of column chromatography on silica gel. This yielded: 1.043 g (1.98 mmol: 30%) of the title compound A and 870 g (1.65 mmol); 25%) of the title compound B.
Compound A: ^{1}H-NMR($CDCl_3$): δ = 0.07 (6H), 0.90 (9H), 1.12-1.20 (3H),1.45-1.67 (5H), 1.71

(3H), 1.81 (1H), 2.24-2.51 (4H), 2.70 (3H), 3.30-3.77 (5H), 3.81-4.00 (1H), 4.17-4.27) (1H), 4.61 (1H), 5.23 (1H), 5.99-6.12 (1H), 7.34 (1H) ppm.
Compound B: ^{1}H-NMR($CDCl_3$): δ = 0.09 (6H), 0.90 (9H), 1.11-1.20 (3H),1.48-1.61 (4H), 1.62 (3H), 1.68-1.90 (2H), 1.22-1.32 (2H), 1.39-1.47 (2H), 2.70 (3H), 3.28-3.65 (5H), 3.80-3.99 (1H), 1.16-4.27 (1H), 4.61 (1H) 5.21 (1H) 5.98-6.12 (1H), 7.33 (1H) ppm.

Example 1h
(2R,6Z,9S,10Z)-2,6-dimethyl-9-[[dimethyl(1,1-dimethylethyl) silyl] oxy]-10-fluoro-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-diene-1-ol

[0090] A solution of 1.043 g (1.98 mmol) of the compound A described for 1 g and 990 mg (3.94 mmol) p-toluene sulfonic acid pyridium salt in 50 ml ethanol was stirred for 2 hours at a temperature of 50 °C. This was then diluted with dichloromethane. The organic phase was washed with a saturated aqueous sodium hydrogen carbonate solution and with a saturated aqueous sodium chloride solution. This was dried by way of sodium sulfate. The thus obtained raw product was cleaned with a mixture of ethylene acetate/hexane by way of column chromatography on silica gel. This yielded: 702 mg (1.58 mmol: 80%) 1h.
^{1}H-NMR($CDCl_3$): δ = 0.09 (6H), 0.91 (9H), 1.10 (3H), 1.72 (3H), 2.28-2.37 (2H), 2.40-2.51 (2H), 2.40-2.51 (2H), 2.70 (3H), 3.35-3.65 (5H), 4.17-4.28 (1H), 5.28 (1H), 6.00-6.13 (1H), 7.34 (1H) ppm.

Example 1i
(2R,6Z,9S,10Z)-2,6-dimethyl-9-[[dimethyl(1,1-dimethylethyl) silyl] oxy]-10-fluoro-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-diene-1-al

[0091] Analogous to example 1d, 698 mg (1.58 mmol; 100%) crude 1i were obtained from 702 mg (1.58 mmol) 1h and this was used in the following stage without a cleaning process.
^{1}H-NMR($CDCl_3$): δ = 0.07 (6H), 0.88 (9H), 1.25 (3H), 1.70 (3H), 2.23-2.48 (4H), 2.69 (3H), 3.44-3.59 (2H), 3.72 (1H), 4.14-4.26 (1H), 5.25 (1H), 5.98-6.11 (1H), 7.31 (1H), 9.61 (1H) ppm.

Example 1k
(3S,6R,7S,8R,12Z,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-1,3,15-tris[(dimethyl(1,1-dimethyl ethyl) silyl] oxy] heptadeca-12,16-diene-7-ol(A)

(3S,6R,7S,8R,12Z,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-1,3,7,15-tris[(dimethyl(1,1-dimethyl ethyl) silyl] oxy] heptadeca-12,16-diene-7-ol(B)

[0092] In a quantity of 20 ml absolute tetrahydrofuran was prepared lithium diisopropyl amide from 473 mg (3.37 mmol) diisopropyl amine and 1.37 ml (3.41 mmol) of a 2.5 molar solution of butyl lithium in hexane. To this was added at -70 °C a solution of 1.273 g (3.16 mmol) (3S)-1,3-bis[(dimethyl ethyl) silyl] oxy]-4,4-dimethyl heptane-5-one in 15 ml tetrahydrofuran and this was stirred further for one hour at between -40 °C and -30 °C. This was cooled again to -70 °C and a solution of 698 mg (1.58 mmol) 1i in 15 ml tetrahydrofuran was added slowly and in drops. This was stirred further for one hour at -70 °C and the reaction mixture was poured on a saturated aqueous ammonium chloride solution. One extracted with ethyl acetate, washed the organic phase with a saturated aqueous sodium chloride solution and dried by way of sodium sulfate. The thus

obtained raw product was cleaned with a mixture of ethylene acetate/hexane by way of a column chromatography on silica gel. This yielded 494 mg (0.59 mmol: 37%) of the title compound A and 464 mg (0.55 mmol; 35%) of the title compound B.
Compound A: ^{1}H-NMR($CDCl_3$): δ = 0.00-0.18 (18H), 0.84-0.99 (27H), 1.05 (3H), 1.08-1.18 (6H), 1.21 (3H), 1.71 (3H), 2.20-2.47 (4H), 2.69 (3H), 3.18-3.36 (3H), 3.50-3.70 (4H) 3.90 (1H), 4.15-4.28 (1H), 5.24 (1H), 5.98-6.12 (1H), 7.32 (1H) ppm.

Compound B: ^{1}H-NMR($CDCl_3$): δ = 0.02-0.15 (18H), 0.85-0.94 (27H), 1.05 (3H), 1.08 (3H), 1.15 (3H), 1.20 (3H), 1.75 (3H), 2.30 (2H), 2.37-2.52 (2H), 2.70 (3H), 3.20-3.74 (7H) 4.09 (1H), 4.17-4.26 (1H), 5.25 (1H), 6.00-6.14 (1H), 7.34 (1H) ppm.

Example 1l
(3S,6R,7S,8R,12Z,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-1,3,7,15-tetrakis ([(dimethyl (1,1-dimethylethyl) silyl] oxy] heptadeca-12,16-diene

[0093] To a solution of 494 mg (0.59 mmol) of the compound A described in 1k and in 30 ml dichloromethane was added at -10 °C 135 pl (1.17 mmol) 2,6-lutidine and 161 µl (0.70 mmol) trifluoromethane sulfonic acid-tert. butyl dimethyl silyl ester. This was stirred further for 2 hours at 0 °C. The reaction mixture was then poured on a saturated aqueous sodium hydrogen carbonate solution. One extracted with dichloromethane, washed the organic phase with a saturated aqueous sodium chloride solution, dried by way of sodium sulfate and concentrated the mixture in a vacuum. The thus obtained raw product was cleaned with a mixture of ethylene acetate/hexane by way of a column chromatography on silica gel. This yielded 527 g (0.55 mmol: 93%) 1l.
^{1}H-NMR($CDCl_3$): δ = 0.00-0.15 (24H), 0.82-0.97 (36H), 1.03 (3H), 1.06 (3H), 1.11 (3H), 1.28 (3H), 1.69 (3H), 2.22-2.46 (4H), 2.70 (3H), 3.18-3.40 (4H), 3.52-3.72 (2H), 3.80 (1H), 3.99 (1H, 4.13-4.27 (1H), 5.22 (1H), 5.99-6.12 (1H), 7.33 (1H) ppm.

Example 1m
(3S,6R,7S,8R,12Z,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-3,7,15-tris[[dimethyl(1,1-dimethyl ethyl) silyl] oxy] heptadeca-12,16-diene-1-ol

[0094] A solution of 527 mg (0.55 mmol) 1l and 128 mg (0.55 mmol) camphor-10-sulfonic acid in 20 ml of a 1:1 mixture consisting of dichloromethane and methanol was stirred for 2 hours at 25 °C. To this was then added an excess quantity of triethyl amine and this was concentrated in a vacuum. The thus obtained raw product was cleaned with a mixture of ethylene acetate / hexane by way of a column chromatography on silica gel. This yielded 404 mg (0.48 mmol: 87%) 1m.
^{1}H-NMR($CDCl_3$): δ = 0.03-0.14 (18H), 0.85-0.95 (27H), 1.06 (3H), 1.08-1.15 (6H), 1.24 (3H), 1.71 (3H), 2.11-2.35 (3H), 2.42 (2H), 2.69 (3H), 3.15-3.40 (4H), 3.59-3.69 (2H) 3.99-4.06 (2H), 4.14-4.25 (1H), 5.21 (1H), 5.99-6.12 (1H), 7.34 (1H) ppm.

Example 1n
(3S,6R,7S,8R,12Z,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-3,7,15-tris[[dimethyl(1,1-dimethyl ethyl) silyl] oxy] heptadeca-12,16-diene-1-al

[0095] Analogous to example 1d, 403 mg (0.48 mmol, 100%) 1n were obtained from 404 mg (0.48 mmol) of the substance described in example 1m. The substance was used for the next stage

without a previous cleaning.

^{1}H-NMR($CDCl_3$): δ = 0.02-0.13 (18H), 0.83-0.92 (27H), 1.02 (3H), 1.09 (3H), 1.11 (3H), 1.39 (3H), 1.71 (3H), 2.10-2.31 (2H), 2.34-2.45 (3H), 2.58-2.63 (1H), 2.71 (3H), 3.14-3.40 (4H), 4.01 (1H), 4.14-4.26 (1H), 4.49 (1H), 5.22 (1H), 5.99-6.12 (1H), 7.34 (1H) ppm.

Example 1o
(3S,6R,7S,8R,12Z,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-3,7,15-tris[[dimethyl(1,1-dimethyl ethyl) silyl] oxy] heptadeca-12,16-dienic acid

[0096] A solution of 403 mg (0.48 mmol) of the substance described in 1n in 15 ml tert.-butanol was reacted with 13.7 ml 2-methyl-2-butene (27.4 mmol). This was then cooled to 2 °C and one added 3.7 ml water, 198 mg (1.44.mmol) sodium dihydrogen phosphate monohydrate, 336 mg sodium chlorite (2.97 mmol) and this was stirred further for 1 hour at 2 °C. This was poured into a saturated sodium thiosulfate solution, was diluted with water and extracted several times with ethyl acetate. The combined organic extracts were dried by way of sodium sulfate and the rest obtained after a filtration and solvent removal was cleaned by way of a chromatography on fine silica gel with a gradient system of n-hexane and ethyl acetate. One obtained 345 mg (0.40 mmol), 84%) 1o.
^{1}H-NMR($CDCl_3$): δ = 0.04-0.15 (18H), 0.86-0.94 (27H), 1.05 (3H), 1.14 (3H), 1.18 (3H), 1.28 (3H), 1.71 (3H), 2.05 (3H), 2.26-2.48 (4H), 2.63-2.71 (1H), 2.72 (3H), 3.10-3.42 (4H), 4.08 (1H), 4.13-4.26 (1H), 4.37 (1H), 5.23 (1H), 6.20-6.33 (1H), 7.33 (1H) ppm.

Example 1p
(3S,6R,7S,8R,12Z,15S,16Z)-3,7-bis[[dimethyl(1,1-dimethylethyl) silyl) oxy]-16-fluoro-15-hydroxy-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-12,16-dienic acid

[0097] A solution of 345 mg (0.40 mmol) 1o in 15 ml tetrahydrofuran was reacted with 6 ml of a 1-molar solution of tetrabutyl ammonium fluoride in tetrahydrofuran. This was stirred further for one hour at 25 °C and the reaction mixture was then poured on an ice-cold, saturated and aqueous ammonium chloride solution. This was then extracted with ethyl acetate and the organic phase was washed with 1-normal hydrochloric acid and a saturated aqueous sodium hydrogen carbonate solution. This was then dried by way of sodium sulfate. The thus obtained raw product (299 mg; 0.40 mmol; 100%) was used in the next phase without a previous cleaning.
^{1}H-NMR($CDCl_3$): δ = 0.03-0.13 (12H), 0.86-0.92 (18H), 1.06 (3H), 1.11 (3H), 1.16 (3H), 1.28 (3H), 1.73 (3H), 2.27-2.59 (6H), 2.71 (3H), 3.08-3.17 (1H), 3.30-3.49 (3H), 4.08 (1H), 4.21-4.30 (1H), 4.37 (1H), 5.28 (1H), 6.28-6.42 (1H), 7.33 (1H) ppm.

Example 1q
4S,7R,8S,9R,13(Z),16S(Z)-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,7,9,13-penta methyl cyclo- hexadec-13-ene-2,6-dione

[0098] To a solution of 299 mg (0.40 mmol) of the compound described in 1p in 4 ml tetrahydrofuran were added 334 µl (2.40 mmol) triethyl amine and 315 µl (2.01 mmol) 2,4,6-trichlorobenzoyl chloride. This was stirred further for 15 minutes at 25 °C and was then diluted with 35 ml toluene. This solution was added in drops over 3 hours to a solution of 510 mg (4.18 mmol) N,N-dimethyl aminopyridine in 100 ml toluene. This was stirred further for one more hour after the adding process was completed. The reaction mixture was then concentrated in a vacuum. According to the column chromatography, one obtained 169 mg (0.23 mmol, 58%) of the title

compound.
^{1}H-NMR($CDCl_3$): δ = 0.02-0.14 (12H), 0.85-0.93 (18H), 1.07 (3H), 1.12 (3H), 1.19-1.24 (6H), 1.67 (3H), 2.00-2.10 (1H), 2.41-2.65 (3H), 2.70 (3H), 2.76-2.88 (1H), 3.14-3.23 (1H), 3.39-3.53 (3H), 4.02 (1H), 4.34 (1H), 5.23 (1H), 5.46-5.56 (1H), 6.09-6.12 (1H, 7.38 (1H) ppm.

Example 1
(4S,7R,8S,9R,13(Z),16S(Z)-4,8-bis[[dimethyl(1,1-dimethylethyl) silyl-oxy]-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,7,9,13-penta methyl cyclo-hexadec-13-ene-2,6-dione

[0099] To a solution of 169 mg (0.23 mmol) of the compound described in 1d in 10 ml tetrahydrofuran were added at 0 °C 530 µl HF-pyridine complex. This was stirred for one hour at 25 °C and 530 µl HF-pyridine complex was added again. The mixture was stirred further for 10 hours at 25 °C. The reaction mixture was then poured on a saturated aqueous sodium chloride solution. This was extracted with dichloromethane, the organic phase was washed with a saturated aqueous sodium chloride solution and then dried by way of sodium sulfate. A column chromatography on silica gel with a mixture of ethyl acetate/hexane yielded 80 mg (0.16 mmol; 69%) of the title compound.
^{1}H-NMR($CDCl_3$): δ = 1.11 (3H), 1.19 (3H), 1.23 (3H), 1.31 (3H), 1.71 (3H), 2.06-2.17 (1H), 2.38-2.68 (4H). 2.70 (3H), 2.73-2.87 (1H), 3.00 (1H), 3.19-3.31 (2H), 3.48 (1H), 3.74-3.84 (2H), 4.12-4.22 (1H), 5.38-5.49 (1H), 6.10-6.13 (1H), 7.38 (1H) ppm.

Example 2
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl-8,8,10,12,16-pentamethyl-4,13,17,-trioxa-bicyclo [14.1.0] heptadecane-5,9-dione (A)

(1R,3S(Z),7S,10R,11S,12R,16S)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl-8,8,10,12,16-pentamethyl-4,13,17,-trioxa-bicyclo [14.1.0] heptadecane-5,9-dione (B)

[0100] A solution of 20 mg (0.04 mmol) of the compound described in example 1 in 2 ml acetonitrile was reacted with 237 µl of a 1M solution of sodium ethylene diamine tetra-acetate. This was cooled to 0 °C and to this was added 440 µl (4.91 mmol) 1,1,1- trifluoroacetone as well as a mixture of 121 mg (0.20 mmol) oxonium and 28 mg (0.33 mmol) sodium hydrogen carbonate. This was stirred further for 2 hours at 2 °C and then poured on a sodium thiosulfate solution. This was then extracted with ethyl acetate, the organic phase was washed with a saturated aqueous sodium chloride solution and then dried by way of sodium sulfate. According to a column chromatography on silica gel with a mixture of ethyl acetate / hexane, one obtained 10 mg (0.019 mmol; 49%) of title compound A as well as 5 mg (0.01 mmol; 24%) of title compound B.
Compound A: ^{1}H-NMR($CDCl_3$): δ = 1.02 (3H), 1.11 (3H), 1.24 (3H), 1.30 (3H), 1.40 (3H), 1.63-1.74 (1H), 1.78-1.86 (1H), 1.99-2.08 (1H), 2.23-2.31 (1H), 2.50-2.56 (1H), 2.61-2.68 (1H), 2.72 (3H), 2.93 (1H), 3.43-3.59 (4H), 3.60-3.66 (1H), 3.72-3.78 (1H), 4.20 (1H), 4.56 (1H), 5.70-5.77 (1H), 6.21-6.32 (1H), 7.38 (1H) ppm.

Compound B: ^{1}H-NMR($CDCl_3$): δ = 1.07 (3H), 1.14 (3H), 1.21 (3H), 1.27 (3H), 1.31 (3H), 1.72-1.81 (1H), 1.83-1.91 (1H), 2.08-2.17 (1H), 2.23-2.31 (1H), 2.57-2.65 (2H), 2.71 (3H), 2.89 (1H), 3.00 (1H), 3.46-3.58 (1H), 3.65 (1H), 3.83-3.90 (1H), 4.18 (1H), 5.78-5.86 (1H), 6.18-6.28 (1H), 7.40 (1H) ppm.

Example 3
4S,7R,8S,9R,13(E),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl-5,5,7,9,13-penta methyl cyclo- hexadec-13-ene-2,6-dione

Example 3a
(2R,6E,9S,10Z)-2,6-dimethyl-9-[[dimethyl(1,1-dimethyl ethyl) silyl] oxy]-10-fluoro-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-diene-1-ol

[0101] Analogous to example 1h, 600 mg (1.35 mmol; 82%) of the title compound were obtained from 870 mg (1.65 mmol) of the compound B described in example 1g.
^{1}H-NMR($CDCl_3$): δ = 0.08-0.12 (6H), 0.91 (9H), 1.09 (3H), 1.63 (3H), 2.27 (2H), 2.44 (2H), 2.70 (3H), 3.37-3.68 (5H), 4.17-4.29 (1H), 5.23 (1H), 5.98-6.12 (1H), 7.33 (1H) ppm.

Example 3b
(2R,6E,9S,10Z)-2,6-dimethyl-9-[[dimethyl(1,1-dimethylethyl) silyl] oxy]-10-fluoro-11-(2-methyl-4-thiazolyl)-3-oxa-undeca-6,10-diene-1-al

[0102] Analogous to example 1d, 596 mg (1.35 mmol, 100% raw) of the title compound were obtained from 600 mg (1.35 mmol) of the compound described in 3a.

Example 3c
(3S,6R,7S,8R,12E,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-1,3,15-tris[[dimethyl(1,1-dimethyl ethyl) silyl] oxy] heptadeca-12,16-diene-7-ol (A)

(3S,6S,7S,8R,12E,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-1,3,7,15-tris[[dimethyl(1,1-dimethyl ethyl) silyl] oxy] heptadeca-12,16-diene-7-ol (B)

[0103] Analogous to example 1k, 464 mg (0.55 mmol; 41%) of title compound A and 388 mg (0.46 mmol; 34%) of title compound B were obtained from 596 mg (1.35 mmol) of the compound described in 3b.

Compound A: ^{1}H-NMR($CDCl_3$): δ = 0.00-0.16 (18H), 0.86-0.99 (27H), 1.05 (3H), 1.11 (3H), 1.15 (3H), 1.22 (3H), 1.62 (3H), 2.25 (2H), 2.41 (2H), 2.53 (1H), 2.69 (3H), 3.18-3.37 (3H), 3.48-3.73 (4H), 3.90 (1H), 4.15-4.28 (1H), 5.21 (1H), 5.98-6.10 (1H), 7.33 (1H) ppm.

Compound B: ^{1}H-NMR($CDCl_3$): δ = 0.00-0.18 (18H), 0.84-0.97 (27H), 1.03 (3H), 1.08 (3H), 1.17 (3H), 1.19 (3H), 2.24 (2H), 2.43 (2H), 2.70 (3H), 3.18-3.28 (2H), 3.42-3.52 (2H), 3.57-3.73 (3H), 4.07 (1H), 4.16-4.28 (1H), 5.22 (1H), 5.99-6.12 (1H), 7.32 (1H) ppm.

Example 3d
(3S,6R,7S,8R,12E,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-1,3,7,15-tetrakis[[dimethyl(1,1-dimethylethyl) silyl] oxy] heptadeca-12,16-diene

[0104] Analogous to example 1l, 485 mg (0.51 mmol; 92%) of the title compound were obtained from 464 mg (0.55 mmol) of the compound A described in 3c.

^{1}H-NMR($CDCl_3$): δ = 0.02-0.13 (24H), 0.82-0.96 (36H), 0.98-1.04 (6H), 1.10 (3H), 1.28 (3H), 1.62 (3H), 2.17 (2H), 2.40 (2H), 2.69 (3H), 3.20 (1H), 3.28-3.39 (3H), 3.52-3.72 (2H), 3.80 (1H), 3.98 (1H), 4.01-4.26 (1H), 5.18 (1H), 5.98-6.11 (1H), 7.31 (1H) ppm.

Example 3e
(3S,6R,7S,8R,12E,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-3,7,15-tris[[dimethyl(1,1-dimethylethyl) silyl] oxy] heptadeca-12,16-diene-1-ol

[0105] Analogous to example 1m, 370 mg (0.44 mmol; 86%) of the title compound were obtained from 485 mg (0.51 mmol) of the compound described in 3d.
^{1}H-NMR($CDCl_3$): δ = 0.02-0.17 (18H), 0.84-0.97 (27H), 1.04 (3H), 1.07-1.14 (6H), 1.22 (3H), 1.61 (3H), 2.17 (2H), 2.41 (2H), 2.70 (3H), 3.20 (1H), 3.30-3.42 (3H), 3.59-3.70 (2H), 4.02 (2H), 4.13-4.29 (1H), 5.18 (1H), 5.98-6.10 (1H), 7.32 (1H) ppm.

Example 3f
(3S,6R,7S,8R,12E,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-3,7,15-tris[[dimethyl(1,1-dimethylethyl) silyl] oxy] heptadeca-12,16-diene-1-al

[0106] Analogous to example 1d, 370 mg (0.44 mmol; 100% raw) of the title compound were obtained from 370 mg (0.44 mmol) of the compound described in 3e.
^{1}H-NMR($CDCl_3$): δ = 0.01-0.15 (18H), 0.82-0.95 (27H), 1.01 (3H), 1.05-1.12 (6H), 1.27 (3H), 1.61 (3H), 2.15 (2H), 2.42 (2H), 2.56-2.67 (1H), 2.70 (3H), 3.17 (1H), 3.28-3.41 (3H), 4.00 (1H), 4.13-4.28 (1H), 4.40 (1H), 5.18 (1H), 5.98-6.11 (1H), 7.32 (1H) ppm.

Example 3g
(3S,6R,7S,8R,12E,15S,16Z)-16-fluoro-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-penta methyl-3,7,15-tris[[dimethyl(1,1-dimethylethyl) silyl] oxy] heptadeca-12,16-dienic acid

[0107] Analogous to example 1o, 302 mg (0.35 mmol; 80%) of the title compound were obtained from 370 mg (0.44 mmol) of the compound described in 3f.
^{1}H-NMR($CDCl_3$): δ = 0.00-0.16 (18H), 0.82-0.98 (27H), 1.05 (3H), 1.10 (3H), 1.15 (3H), 1.21 (3H), 1.61 (3H), 2.15 (2H), 2.25-2.53 (3H), 2.63-2.76 (1H), 2.72 (3H), 3.17 (1H), 3.28-3.44 (3H), 4.07 (1H), 4.16-4.28 (1H), 4.34 (1H), 5.21 (1H), 6.07-6.20 (1H), 7.35 (1H) ppm.

Example 3h
(3S,6R,7S,8R,12E,15S,16Z)-3,7-bis[[dimethyl(1,1-dimethylethyl) silyl]-16-fluoro-15-hydroxy-17-(2-methyl-4-thiazolyl)-9-oxa-5-oxo-4,4,6,8,12-pentamethyl-12,16-dienic acid

[0108] Analogous to example 1p, 260 mg (0.35 mmol; 100% raw) of the title compound were obtained from 302 mg (0.35 mmol) of the compound described in 3g.
^{1}H-NMR($CDCl_3$): δ = 0.02-0.13 (12H), 0.83-0.98 (18H), 1.04 (3H), 1.08-1.17 (6H), 1.24 (3H), 1.63 (3H), 2.16 (1H), 2.22-2.35 (1H), 2.42-2.69 (3H), 2.69 (3H), 3.11 (1H), 3.30-3.47 (3H), 3.99-4.14 (1H), 3.27-3.47 (2H), 5.22 (1H), 6.18-6.32 (1H), 7.33 (1H) ppm.

Example 3i
(4S,7R,8S,9R,13(E),16S(Z)-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl)

ethenyl)-5,5,7,9,13-penta methyl cyclo-hexadec-13-ene-2,6-dione
[0109] Analogous to example 1q, 175 mg (0.24 mmol; 69%) of the title compound were obtained from 260 mg (0.35 mmol) of the compound described in 3h.
^{1}H-NMR($CDCl_3$): δ = 0.03-0.16 (12H), 0.85-0.94 (18H), 1.06 (3H), 1.09-1.16 (6H), 1.18 (3H), 1.63 (3H), 2.02-2.29 (2H), 2.38-2.46 (1H), 2.53-2.63 (2H), 2.67-2.82 (1H), 2.68 (3H), 3.08 (1H), 3.33-3.48 (2H), 3.55-3.62 (1H), 4.00 (1H), 4.43 (1H), 5.29 (1H), 5.46-5.57 (1H), 6.12-6.24 (1H), 7.38 (1H) ppm.

Example 3
4S,7R,8S,9R,13(E),16S(Z)-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,7,9,13-penta methyl cyclo-hexadec-13-ene-2,6-dione

[0110] Analogous to example 1, 85 mg (0.17 mmol, 71%) of the title compound were obtained from 175 mg (0.24 mmol) of the compound described in 3i.
^{1}H-NMR($CDCl_3$): δ = 1.06 (3H), 1.17 (3H), 1.24 (3H), 1.30 (3H), 1.69 (3H), 2.23 (2H), 2.48-2.61 (2H), 2.61-2.77 (2H), 2.70 (3H), 3.28-3.45 (3H), 3.52 (1H), 3.67-3.79 (2H), 4.21 (1H), 5.23 (1H), 5.53-5.63 (1H), 6.12-6.26 (1H), T.39 /sic/ (1H) ppm.

Example 4
(1S,3S(Z),7S,10R,11S,12R,16S)-7,11-dihydroxy-3-(1-fluoro-2(2-methyl-4-thiazolyl) ethenyl-8,8,10,12,16-pentamethyl-4,13,17-trioxa-bicyclo [14.1.0] heptadecane-5,9-dione (A)

(1R,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2(2-methyl-4-thiazolyl) ethenyl-8,8,10,12,16-pentamethyl-4,13,13,17-trioxa-bicyclo [14.1.0] heptadecane-5,9-dione (B).

[0111] Analogous to example 2, 19 mg (0.037 mmol, 37%) of title compound A and 14 mg (0.027 mmol; 27%) of title compound B were obtained from 50 mg (0.10 mmol) of the compound described in example 3.
Compound A: ^{1}H-NMR($CDCl_3$): δ = 1.11 (3H), 1.17-1.25 (6H), 1.28 (3H), 1.36 (3H), 1.52-1.61 (1H), 2.08-2.22 (3H), 2.45 (1H), 2.69 (3H), 2.76-2.85 (1H), 2.98-3.08 (2H), 3.17-3.37 (2H), 3.46-3.60 (2H), 3.69 (1H), 4.31 (1H), 5.61-5.73 (1H), 6.16-6.28 (1H), 7.39 (1H) ppm.

Compound B: ^{1}H-NMR($CDCl_3$): δ = 1.02 (3H), 1.17 (3H), 1.22 (3H), 1.29 (3H), 1.36 (3H), 1.55-1.79 (3H), 1.95-2.35 (3H), 2.47-2.63 (2H), 2.69 (3H), 2.94 (1H), 3.09 (1H), 3.16-3.27 (1H), 3.38-3.48 (1H), 3.54-3.69 (3H), 4.16 (1H), 4.32 (1H), 5.62-5.73 (1H), 6.19-6.32 (1H), 7.39 (1H) ppm.

Patent claims

1. Epothilone derivatives of the general formula I

/formula/

where
R^{1a}, R^{1b} are identical or different and are hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or jointly a $(CH_2)_m$ group with m = 1,2,3,4 or 5, or a -(CH_2)-O-(CH_2)-group,
R2a, R^{2b} are identical or different and are hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, -$(CH_2)_r$-C ≡ C-$(CH_2)_p$-R^9, -
$(CH_2)_r$-C = C-$CH_2)_p$-R^9,
r equals 0 to 4,
p equals 0 to 3,
R^9 is hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, C_1-C_{10} acyl, or - when p>0 - also a group OR^{10},
R^{10} is hydrogen, a protective group PG^{10},
R^{3a} is hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,
R^{3b}, OH, OPG^3
R^4 is hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,
R^5 is hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, halogen, cyano, $(CH_2)_s$-T, in which case s is 1, 2, 3 or 4,
T stands for OR^{11} or halogen,
R^{11} stands for hydrogen or PG^{11},
R^6, R^7 each represent a hydrogen atom, together an additional linkage or an oxygen atom,
G is a group

/diagram/

a bi- or tricyclic aryl rest,
R^{12} is hydrogen, halogen, CN, C_1-C_{20}-alkyl, aryl, C_7-C_{20} aralkyl, all of which can be substituted,
X is an oxygen atom, two alkoxy groups OR^{13}, a C_2-C_{10} alkylene-α,ω-dioxy group which can be linear or branched, H/OR^{14} or a grouping $CR^{15}R^{16}$,
in which case
R^{13} is a C_1-C_{20} alkyl rest,
R^{14} is hydrogen or a protective group PG^{14},
R^{15}, R^{16} are identical or different and stand for hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl rest,
A-Y is a group O-C(=O), O-CH_2, CH_2C(-O), NR^{17}-C(=O), NR^{17}-SO_2,
R^{17} stands for hydrogen, C_1-C_{10} alkyl
Z is an oxygen atom or H/OR^{18},
in which case
R^{18} is a hydrogen or a protection group PG^{18},
R^8 is OH or OPG^8,
Hal is halogen, preferably fluorine, chlorine or bromine,
with the exception of those compounds, in which R^{2a} is hydrogen and R^{2b} stands for hydrogen, alkyl or aryl and simultaneously
R^5 is hydrogen, alkyl or aryl and simultaneously

A-Y is a grouping O-C(=O), O-CH_2 or NR^{17}-C(=O) and simultaneously
G stands for a bi- or tricyclic aryl rest or a grouping X=(CR^{12}), in which case all other rests may have the indicated meaning.

2. Epothilone derivatives of the general formula I in accordance with claim 1, i.e.,
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,7,9,13-penta-methyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12,16-penta methyl-4,13,17-trioxa bicyclo [14.1.0] heptadecan-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12,16-tetra-methyl-4,13,17-trioxa bicyclo [14.1.0] heptadecan-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,l3-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,10,12,16-penta methyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-h-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-pyridyl) ethenyl)-5,5,7,9,13-penta methyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-pyridyl) ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-fluoro-2-(2-pyridyl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-pyridyl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-

1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-oza-13,17-dioxa bicyclo[14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,10,12,16-pentamethyl-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-methyl oxazol4-yl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-pyridyl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-fluoro-2-(2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-fluoro-2-(2-pyridyl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,7,9,13-penta-methyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxabicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methylexazol-4-yl) ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-

8,8,10,12,16-pentamethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-6-(1-chloro-2-(2-pyridyl) ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-pyridyl) ethenyl)-8,8,10,12,16-pentamethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-7-ethyl-16-(1-chloro-2-(2-pyridyl) ethenyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-pyridyl) ethenyl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo[14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-1-aza-10-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-chloro-2-(2-methyl oxazoltyl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl oxazol-4-yl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-pyridyl) ethenyl)-1-aza-10-oxa-

5,5,7,9,13-pentamethyl cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-pyridyl) ethenyl)-8,8,10,12,16-pentamethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-7-ethyl-16-(1-chloro-2-(2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-10-ethyl-3-(1-chloro-2-(2-pyridyl) ethenyl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7,9,13-trimethyl-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadeca-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-7-ethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-10-ethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-7,9,13-trimethyl-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10,12,16-trimethyl-8,8(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] heptadeca-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-7-ethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-10-ethy(-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-enel-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-7,9,13-trimethyl-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-deca-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-7-ethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-10-ethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-

5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-7(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-7,9,13-trimethyl-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10,12,16-trimethyl-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-deca-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-7-ethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-10-ethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo[14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo[14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.O] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,l3-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.O] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-

thiazolyl) ethenyl)-7-(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.O] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazoly (ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.O) heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-in-1yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(prop-2-in-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(prop-2-in-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)7-(prop-2-ine-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-timethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-en-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(but-2-ine-1yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(but-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-

2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(11-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl oxazol-4-yl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl) ethenyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl) ethenyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ine-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-5-benzoxazolyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ine-1-yl-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.

(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-1-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ine-1yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ene-1-yl)-1-aza-10 oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo-[14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,SS,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ine-1yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzoxazolyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzoxazolyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-5-benzothiazolyl)-10-

(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [141.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ene-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ine-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(prop-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(prop-2-ine-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ene-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-14,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ene-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ene-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzethiazolyl)-10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ene-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-

10-(but-2-ene-1-yl)-8,8-(1,3-trimethylene)-4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ine-1-yl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ine-1-yl)-8,8,12,16-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-1,10-dioxa-9,13-dimethyl-16-(2-methyl-5-benzothiazolyl)-7-(but-2-ine-1-yl)-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene)-4,13,17-trioxa bicyclo (14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9R,13(Z),16S(Z))-4,8-dihydroxy-9,13-dimethyl-16-(2-methyl-5-benzo thiazolyl)-7-(but-2-ine-1-yl)-1-aza-10-oxa-5,5-(1,3-trimethylene) cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12R,16R)-7,11-dihydroxy-12,16-dimethyl-3-(2-methyl-5-benzothiazolyl)-10-(but-2-ine-1-yl)-8,8-(1,3-trimethylene-)4-aza-13,17-dioxa bicyclo [14.1.0] hepta-decane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-chloro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-13-chloro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-fluoro-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-fluoro-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-allyl-13-chloro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-

thiazolyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-chloro-16-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-enee-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,1OR,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-trimethylene-1,10-dioxa-7,9-dimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-trimethylene-1,10-dioxa-7,9-dimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-(chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-oxazolyl) enyl)-8,8,10,12-tetramethyl-4,13,17-trioxabicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-7-ethyl-13-chloro-16-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-(chloro-7,11-dihydroxy-7-ethyl-3-(1-chloro-2-(2-methyl-2-

pyridyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-7-ethyl-3-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-7-ethyl-13-chloro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-7-allyl-13-chloro-16-(2-methyl-5-benzothiazolyl)-1,10-dioxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,1OR,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzoxazolyl)-1,10-dioxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-

tetramethyl-4,13,17-trioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa 5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-chloro-1(3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-13-chloro-1(3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-13-fluoro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-fluoro-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-fluoro-10-ethyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-allyl-13-chloro-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-10-allyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-13-chloro-16-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(E),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(E),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,1OR,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl)

ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-trimethylene-1-aza-10-oxa-7,9-dimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,1OR,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,SS,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-5,5-trimethylene-1-aza-10-oxa-7,9-dimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-59-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-chloro-2-(2-methyl-4-thiazolyl) ethenyl)-8,8-trimethylene-10,12-dimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-4-oxazolyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-13-chloro-16-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(1-fluoro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S(Z))-4,8-dihydroxy-7-ethyl-13-chloro-16-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S(Z),7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-7-ethyl-3-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S(Z),7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-7-ethyl-3-(1-chloro-2-(2-methyl-2-pyridyl) ethenyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,1OR,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-

5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-7-ethyl-13-chloro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-10-ethyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-7-allyl-13-chloro-16-(2-methyl-5-benzothiazolyl)-1-aza-10-oxa-5,5,9-trimethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-trimethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-10-allyl-3-(2-methyl-5-benzothiazolyl)-8,8,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)4,8-dihydroxy-13-fluoro-16-(2-methyl-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-fluoro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(4S,7R,8S,9S,13E,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl(-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-13-chloro-16-(2-methyl-5-benzoxazolyl)-1-aza-10-oxa-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione.
(1S,3S,7S,10R,11S,12S,16S)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzoxazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.
(1R,3S,7S,10R,11S,12S,16R)-16-chloro-7,11-dihydroxy-3-(2-methyl-5-benzothiazolyl)-8,8,10,12-tetramethyl-4-aza-13,17-dioxa bicyclo [14.1.0] heptadecane-5,9-dione.

3. Pharmaceutical preparations that contain at least one epothilone derivative of the general formula I in accordance with claim 1 as well as a pharmaceutically compatible carrier.

4. The use of the compounds of general formula I in accordance with claim 1 for the preparation of drugs.

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